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Attorneys for Plaintiff
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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

THERAPEUTICSMD, INC.,

Plaintiff,

v.

**AMNEAL PHARMACEUTICALS, INC.,
AMNEAL PHARMACEUTICALS, LLC,
and AMNEAL PHARMACEUTICALS OF
NEW YORK LLC,**

Defendants.

**Civil Action No. 20-5256 (FLW)(TJB)
Civil Action No. 20-14933 (FLW)(TJB)**

**THIRD AMENDED COMPLAINT
FOR PATENT INFRINGEMENT¹**

(Filed Electronically)

¹ Plaintiff TherapeuticsMD, Inc. files this Third Amended Complaint for Patent Infringement with Defendants Amneal Pharmaceuticals, Inc., Amneal Pharmaceuticals, LLC, and Amneal Pharmaceuticals of New York LLC's consent pursuant to Fed. R. Civ. P. 15(a)(2).

Plaintiff TherapeuticsMD, Inc. (“TherapeuticsMD”), by its undersigned attorneys, for its Complaint against defendants Amneal Pharmaceuticals, Inc. (“Amneal Inc.”), Amneal Pharmaceuticals, LLC (“Amneal LLC”), and Amneal Pharmaceuticals of New York LLC (“Amneal NY”) (together, “Amneal” or “Defendants”), alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. § 100, *et seq.*, arising from the filing of Abbreviated New Drug Application (“ANDA”) No. 214293 (“Amneal’s ANDA”) with the United States Food and Drug Administration (“FDA”) seeking approval to commercially market a generic version of TherapeuticsMD’s BIJUVA® drug product (“Amneal’s Proposed Product”) before the expiration of United States Patent Nos. 8,633,178 (the “178 patent”); 8,846,648 (the “648 patent”); 8,846,649 (the “649 patent”); 8,987,237 (the “237 patent”); 8,993,548 (the “548 patent”); 8,993,549 (the “549 patent”); 9,006,222 (the “222 patent”); 9,114,145 (the “145 patent”); 9,114,146 (the “146 patent”); 9,301,920 (the “920 patent”); 10,052,386 (the “386 patent”); 10,206,932 (the “932 patent”); 10,639,375 (the “375 patent”); 10,675,288 (the “288 patent”); 11,033,626 (the “626 patent”), 11,103,513 (the “513 patent”), 11,103,516 (the “516 patent”), and 11,110,099 (the “099 patent”) (collectively, “the patents-in-suit”), all owned by TherapeuticsMD.

The Parties

2. Plaintiff TherapeuticsMD is a women’s healthcare company committed to creating and commercializing innovative products to support women from pregnancy prevention through menopause. TherapeuticsMD focuses on, and invests heavily in, the development and commercialization of health solutions that enable new standards of care for women.

TherapeuticsMD is a corporation organized and existing under the laws of the State of Nevada, having a principal place of business at 951 Yamato Road, Suite 220, Boca Raton, Florida 33431.

3. On information and belief, Defendant Amneal Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 400 Crossing Boulevard, Bridgewater, New Jersey 08807.

4. On information and belief, Defendant Amneal LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 400 Crossing Boulevard, Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal LLC is a wholly owned subsidiary of Amneal Inc.

5. On information and belief, Defendant Amneal NY is a limited liability company organized and existing under the laws of the State of Delaware, having a place of business at 400 Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is a wholly owned subsidiary of Amneal LLC.

The Patents-in-Suit

6. On January 21, 2014, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued the ’178 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’178 patent is attached hereto as Exhibit A.

7. On September 30, 2014, the USPTO duly and lawfully issued the ’648 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’648 patent is attached hereto as Exhibit B.

8. On September 30, 2014, the USPTO duly and lawfully issued the ’649 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to

TherapeuticsMD as assignee of the inventors. A copy of the '649 patent is attached hereto as Exhibit C.

9. On March 24, 2015, the USPTO duly and lawfully issued the '237 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '237 patent is attached hereto as Exhibit D.

10. On March 31, 2015, the USPTO duly and lawfully issued the '548 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '548 patent is attached hereto as Exhibit E.

11. On March 31, 2015, the USPTO duly and lawfully issued the '549 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '549 patent is attached hereto as Exhibit F.

12. On April 14, 2015, the USPTO duly and lawfully issued the '222 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '222 patent is attached hereto as Exhibit G.

13. On August 25, 2015, the USPTO duly and lawfully issued the '145 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '145 patent is attached hereto as Exhibit H.

14. On August 25, 2015, the USPTO duly and lawfully issued the '146 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to

TherapeuticsMD as assignee of the inventors. A copy of the '146 patent is attached hereto as Exhibit I.

15. On April 5, 2016, the USPTO duly and lawfully issued the '920 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '920 patent is attached hereto as Exhibit J.

16. On August 21, 2018, the USPTO duly and lawfully issued the '386 patent, entitled, "Progesterone Formulations," to TherapeuticsMD as assignee of the inventors. A copy of the '386 patent is attached hereto as Exhibit K.

17. On February 19, 2019, the USPTO duly and lawfully issued the '932 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '932 patent is attached hereto as Exhibit L.

18. On May 5, 2020, the USPTO duly and lawfully issued the '375 patent, entitled, "Progesterone Formulations," to TherapeuticsMD as assignee of the inventors. A copy of the '375 patent is attached hereto as Exhibit M.

19. On June 9, 2020, the USPTO duly and lawfully issued the '288 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '288 patent is attached hereto as Exhibit N.

20. On June 15, 2021, the USPTO duly and lawfully issued the '626 patent, entitled, "Progesterone Formulations Having A Desirable PK Profile" to TherapeuticsMD, Inc. as assignee of the inventors. A copy of the '626 patent is attached hereto as Exhibit O.

21. On August 31, 2021, the USPTO duly and lawfully issued the '513 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies" to

TherapeuticsMD, Inc. as assignee of the inventors. A copy of the '513 patent is attached hereto as Exhibit P.

22. On August 31, 2021, the USPTO duly and lawfully issued the '516 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies" to TherapeuticsMD, Inc. as assignee of the inventors. A copy of the '516 patent is attached hereto as Exhibit Q.

23. On September 7, 2021, the USPTO duly and lawfully issued the '099 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies" to TherapeuticsMD, Inc. as assignee of the inventors. A copy of the '099 patent is attached hereto as Exhibit R.

The BIJUVA® Drug Product

24. TherapeuticsMD holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for estradiol and progesterone capsules (NDA No. 210132), which it sells under the trade name BIJUVA®. BIJUVA® is an FDA-approved medication indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

25. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions and formulations comprising estradiol and progesterone, pharmaceutical compositions comprising progesterone, and methods of use of pharmaceutical compositions comprising estradiol and progesterone.

26. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to BIJUVA®.

Jurisdiction and Venue

27. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

28. On information and belief, one or more acts related to Amneal's preparation of Amneal's ANDA and the preparation of Amneal's written certifications to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Amneal's Paragraph IV Certification(s)'), set forth in Amneal's ANDA were conducted in this District and/or will be conducted in the District.

29. On information and belief, upon FDA approval of Amneal's ANDA, Amneal intends to commercially manufacture, import, market, offer for sale, and/or sell Amneal's Proposed Product throughout the United States including in this Judicial District.

30. On information and belief, Amneal is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. This Judicial District is a likely destination for the generic drug products described in ANDA No. 214293. On information and belief, Amneal also prepares and/or aids in the preparation and submission of ANDAs to the FDA.

31. The Court has personal jurisdiction over Amneal LLC by virtue of, *inter alia*, its continuous and systematic contacts with the State of New Jersey. On information and belief, Amneal LLC's principal place of business is in Bridgewater, New Jersey. On information and belief, Amneal LLC is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business I.D. No. 0600211542. On information and belief, Amneal LLC is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler, under Registration No. 5002991. On

information and belief, Amneal LLC has purposefully conducted and continues to conduct business in this Judicial District.

32. This Court has personal jurisdiction over Amneal NY because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its affiliate, agent, and/or alter ego, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the State of New Jersey as a pharmacy wholesaler; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC. On information and belief, Amneal NY has a place of business at 400 Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler, under Registration No. 5003663. On information and belief, Amneal NY purposefully has conducted and continues to conduct business in this Judicial District.

33. This Court has personal jurisdiction over Amneal Inc. because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its subsidiaries, agents, and/or alter egos, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the State of New Jersey as a pharmacy wholesaler, and Amneal NY, a company that has a place of business in the State of New Jersey and is registered with the State of New Jersey as a drug manufacturer and wholesaler; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC and/or Amneal NY.

34. On information and belief, Amneal Inc.’s executive offices are located in Bridgewater, New Jersey. On information and belief, Amneal Inc. owns or leases numerous properties throughout New Jersey for the purposes of manufacturing, research and development, warehousing, and packaging. (*See* Amneal Pharmaceuticals, Inc. Securities and Exchange Commission Form 10-K (for the fiscal year ended December 31, 2019) (“Amneal Inc. Form 10-K”) at 34.)

35. On information and belief, Amneal Inc. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Amneal Inc. derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. Amneal Inc.’s Form 10-K filing states, “[o]ur Generics segment includes approximately 250 product families covering an extensive range of dosage forms and delivery systems . . . [and] 111 products either approved but not yet launched or pending FDA approval.” (Amneal Inc. 2020 Form 10-K at 6.) On information and belief, Amneal Inc. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

36. This Court has personal jurisdiction over Amneal because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and has sent notice of that infringement to TherapeuticsMD. On information and belief, Amneal intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to TherapeuticsMD in New Jersey and in this Judicial District. For example, on information and belief, Amneal will work towards the regulatory approval, manufacturing, use, importation, marketing, sale, offer for sale, and

distribution of generic pharmaceutical products, including Amneal's ANDA Product, throughout the United States, including in New Jersey and in this Judicial District, before the expiration of the patents-in-suit.

37. Amneal LLC has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., Azurity Pharmaceuticals, Inc. v. Amneal Pharmaceuticals LLC*, No. 21-08717 (D.N.J.); *Cubist Pharmaceuticals LLC v. Amneal Pharmaceuticals, LLC, et al.*, No. 19-15439 (D.N.J.); *Senju Pharmaceutical Co., et al. v. Amneal Pharmaceuticals LLC et al.*, No. 18-05571 (D.N.J.); *BTG International Limited, et al. v. Actavis Laboratories FL, Inc., et al.*, No. 15- 05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.); *Novo Nordisk Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, et al.*, No. 12-05064 (D.N.J.).

38. Amneal LLC has further availed itself of the jurisdiction of this Court by initiating litigation in this Judicial District. *See, e.g., Amneal Pharmaceuticals LLC v. Reckitt Benckiser Pharmaceuticals, Inc., et al.*, No. 15-08864 (D.N.J.).

39. Amneal NY has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., Cubist Pharmaceuticals LLC v. Amneal Pharmaceuticals, LLC, et al.*, No. 19-15439 (D.N.J.); *BTG International Limited et al. v. Actavis Laboratories FL, Inc.. et al.*, No. 15-05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.); *Novo Nordisk Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.).

Amneal Pharmaceuticals, LLC, et al., No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v.*

Amneal Pharmaceuticals, LLC, et al., No. 12-05064 (D.N.J.).

40. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

Acts Giving Rise To This Suit

41. Pursuant to Section 505 of the FFDCA, Amneal’s ANDA seeks FDA approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of 1 mg/100 mg (estradiol/progesterone) capsules before the patents-in-suit expire.

42. No earlier than March 17, 2020, TherapeuticsMD received a letter from Amneal (“Amneal’s First Notice Letter”), notifying TherapeuticsMD that Amneal had submitted ANDA No. 214293 seeking approval to engage in the commercial manufacture, use, and/or sale of 1 mg/100 mg (estradiol/progesterone) capsules prior to the expiration of several patents covering TherapeuticsMD’s BIJUVA® drug product. Amneal’s First Notice Letter alleges that the claims of the ’178 patent, the ’648 patent, the ’649 patent, the ’237 patent, the ’548 patent, the ’549 patent, the ’222 patent, the ’145 patent, the ’146 patent, the ’920 patent, the ’386 patent, and the ’932 patent are invalid and/or will not be infringed by the activities described in Amneal’s ANDA.

43. No earlier than July 17, 2020, TherapeuticsMD received a second letter from Amneal (“Amneal’s Second Notice Letter”), notifying TherapeuticsMD that Amneal was seeking approval to engage in the commercial manufacture, use, and/or sale of 1 mg/100 mg (estradiol/progesterone) capsules prior to the expiration of additional patents covering TherapeuticsMD’s BIJUVA® drug product. Amneal’s Second Notice Letter alleges that the claims of the ’375 patent and the ’288 patent are invalid and/or will not be infringed by the activities described in Amneal’s ANDA.

44. No earlier than November 17, 2020, TherapeuticsMD received a third letter from Amneal (“Amneal’s Third Notice Letter”), notifying TherapeuticsMD that Amneal was seeking approval to engage in the commercial manufacture, use, and/or sale of 1 mg/100 mg (estradiol/progesterone) capsules prior to the expiration of an additional patent covering TherapeuticsMD’s BIJUVA® drug product. Amneal’s Third Notice Letter alleges that the claims of United States Patent No. 10,806,740 are invalid and/or will not be infringed by the activities described in Amneal’s ANDA.

45. No earlier than October 13, 2021, TherapeuticsMD received a fourth letter from Amneal (“Amneal’s Fourth Notice Letter”), notifying TherapeuticsMD that Amneal was seeking approval to engage in the commercial manufacture, use, and/or sale of 1 mg/100 mg (estradiol/progesterone) capsules prior to the expiration of the ’626 patent, the ’513 patent, the ’516 patent, and the ’099 patent. Amneal’s Fourth Notice Letter alleges that the claims of the ’626 patent, the ’513 patent, the ’516 patent, and the ’099 patent are invalid and/or will not be infringed by the activities described in Amneal’s ANDA.

46. On information and belief, following FDA approval of Amneal’s ANDA, Amneal will make, use, offer to sell, or sell Amneal’s Proposed Product throughout the United States, or import such generic products into the United States.

47. On information and belief, the proposed label or proposed package insert for Amneal’s Proposed Product states that it is indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

48. On information and belief, in connection with the filing of its ANDA as described above, Amneal provided Amneal’s Paragraph IV Certification(s) alleging, *inter alia*, that the

claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA.

Count I: Infringement of the '178 Patent

49. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

50. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '178 patent.

51. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

52. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '178 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

53. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '178 patent.

54. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '178 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

55. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '178 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will

intentionally encourage acts of direct infringement with knowledge of the '178 patent and knowledge that its acts are encouraging infringement.

56. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '178 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '178 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

57. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '178 patent is not enjoined.

58. TherapeuticsMD does not have an adequate remedy at law.

59. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '648 Patent

60. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

61. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '648 patent.

62. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

63. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '648 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

64. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '648 patent.

65. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '648 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

66. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '648 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '648 patent and knowledge that its acts are encouraging infringement.

67. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '648 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '648 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

68. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '648 patent is not enjoined.

69. TherapeuticsMD does not have an adequate remedy at law.

70. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '649 Patent

71. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

72. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '649 patent.

73. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

74. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '649 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

75. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '649 patent.

76. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '649 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

77. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '649 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '649 patent and knowledge that its acts are encouraging infringement.

78. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '649 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '649 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

79. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '649 patent is not enjoined.

80. TherapeuticsMD does not have an adequate remedy at law.

81. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '237 Patent

82. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

83. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial

manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '237 patent.

84. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

85. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '237 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

86. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '237 patent.

87. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '237 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

88. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '237 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '237 patent and knowledge that its acts are encouraging infringement.

89. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '237 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that

Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '237 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

90. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '237 patent is not enjoined.

91. TherapeuticsMD does not have an adequate remedy at law.

92. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '548 Patent

93. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

94. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '548 patent.

95. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

96. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '548 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

97. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '548 patent.

98. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '548 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

99. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '548 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '548 patent and knowledge that its acts are encouraging infringement.

100. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '548 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '548 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

101. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '548 patent is not enjoined.

102. TherapeuticsMD does not have an adequate remedy at law.

103. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VI: Infringement of the '549 Patent

104. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

105. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '549 patent.

106. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

107. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '549 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

108. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '549 patent.

109. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '549 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

110. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '549 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '549 patent and knowledge that its acts are encouraging infringement.

111. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '549 patent under 35 U.S.C. § 271(c) by

making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '549 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

112. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '549 patent is not enjoined.

113. TherapeuticsMD does not have an adequate remedy at law.

114. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VII: Infringement of the '222 Patent

115. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

116. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '222 patent.

117. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

118. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '222 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

119. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '222 patent.

120. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '222 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

121. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '222 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '222 patent and knowledge that its acts are encouraging infringement.

122. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '222 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '222 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

123. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '222 patent is not enjoined.

124. TherapeuticsMD does not have an adequate remedy at law.

125. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VIII: Infringement of the '145 Patent

126. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

127. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '145 patent.

128. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

129. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '145 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

130. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '145 patent.

131. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '145 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

132. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '145 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '145 patent and knowledge that its acts are encouraging infringement.

133. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '145 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '145 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

134. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '145 patent is not enjoined.

135. TherapeuticsMD does not have an adequate remedy at law.

136. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IX: Infringement of the '146 Patent

137. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

138. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '146 patent.

139. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

140. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before

the expiration of the '146 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

141. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '146 patent.

142. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '146 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

143. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '146 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '146 patent and knowledge that its acts are encouraging infringement.

144. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '146 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '146 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

145. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '146 patent is not enjoined.

146. TherapeuticsMD does not have an adequate remedy at law.

147. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count X: Infringement of the '920 Patent

148. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

149. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '920 patent.

150. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

151. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '920 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

152. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '920 patent.

153. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '920 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

154. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '920 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will

intentionally encourage acts of direct infringement with knowledge of the '920 patent and knowledge that its acts are encouraging infringement.

155. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '920 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '920 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

156. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '920 patent is not enjoined.

157. TherapeuticsMD does not have an adequate remedy at law.

158. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XI: Infringement of the '386 Patent

159. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

160. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '386 patent.

161. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

162. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '386 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

163. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '386 patent.

164. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '386 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

165. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '386 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '386 patent and knowledge that its acts are encouraging infringement.

166. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '386 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '386 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

167. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '386 patent is not enjoined.

168. TherapeuticsMD does not have an adequate remedy at law.

169. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XII: Infringement of the '932 Patent

170. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

171. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '932 patent.

172. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

173. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '932 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

174. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '932 patent.

175. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '932 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

176. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '932 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '932 patent and knowledge that its acts are encouraging infringement.

177. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '932 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '932 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

178. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '932 patent is not enjoined.

179. TherapeuticsMD does not have an adequate remedy at law.

180. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XIII: Infringement of the '375 Patent

181. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

182. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

183. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '375 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

184. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '375 patent.

185. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '375 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

186. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '375 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '375 patent and knowledge that its acts are encouraging infringement.

187. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '375 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '375 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

188. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '375 patent is not enjoined.

189. TherapeuticsMD does not have an adequate remedy at law.

190. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XIV: Infringement of the '288 Patent

191. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

192. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

193. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '288 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

194. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '288 patent.

195. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '288 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

196. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '288 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will

intentionally encourage acts of direct infringement with knowledge of the '288 patent and knowledge that its acts are encouraging infringement.

197. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '288 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '288 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

198. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '288 patent is not enjoined.

199. TherapeuticsMD does not have an adequate remedy at law.

200. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XV: Infringement of the '626 Patent

201. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

202. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '626 patent.

203. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

204. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '626 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

205. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '626 patent.

206. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '626 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

207. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '626 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '626 patent and knowledge that its acts are encouraging infringement.

208. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '626 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '626 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

209. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '626 patent is not enjoined.

210. TherapeuticsMD does not have an adequate remedy at law.

211. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XVI: Infringement of the '513 Patent

212. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

213. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '513 patent.

214. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

215. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '513 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

216. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '513 patent.

217. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '513 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

218. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '513 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '513 patent and knowledge that its acts are encouraging infringement.

219. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '513 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '513 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

220. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '513 patent is not enjoined.

221. TherapeuticsMD does not have an adequate remedy at law.

222. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XVII: Infringement of the '516 Patent

223. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

224. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial

manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '516 patent.

225. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

226. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '516 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

227. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '516 patent.

228. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '516 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

229. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '516 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '516 patent and knowledge that its acts are encouraging infringement.

230. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '516 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that

Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '516 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

231. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '516 patent is not enjoined.

232. TherapeuticsMD does not have an adequate remedy at law.

233. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XVIII: Infringement of the '099 Patent

234. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

235. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '099 patent.

236. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's First Notice Letter to TherapeuticsMD.

237. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '099 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

238. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '099 patent.

239. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '099 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

240. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '099 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '099 patent and knowledge that its acts are encouraging infringement.

241. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '099 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '099 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

242. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '099 patent is not enjoined.

243. TherapeuticsMD does not have an adequate remedy at law.

244. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff TherapeuticsMD respectfully requests the following relief:

- (A) A Judgment that Amneal has infringed the patents-in-suit by submitting ANDA No. 214293;
- (B) A Judgment that Amneal has infringed, and that Amneal's making, using, offering to sell, selling, or importing Amneal's Proposed Product will infringe one or more claims of the patents-in-suit;
- (C) An Order that the effective date of FDA approval of ANDA No. 214293 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;
- (D) Preliminary and permanent injunctions enjoining Amneal and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Amneal's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;
- (E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Amneal, its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from practicing any of the claimed inventions of the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;
- (F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product will directly infringe, induce, and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Amneal has committed any acts with respect to the claimed inventions of the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding TherapeuticsMD damages for such acts;

(H) If Amneal engages in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product before the expiration of the patents-in-suit, a Judgment awarding damages to TherapeuticsMD resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding TherapeuticsMD its attorneys' fees incurred in this action;

(K) A Judgment awarding TherapeuticsMD its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: December 8, 2021

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EXHIBIT A



US008633178B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 8,633,178 B2
(45) **Date of Patent:** Jan. 21, 2014

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Neda Irani**, Palm Beach Garden, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/684,002**(22) Filed: **Nov. 21, 2012**(65) **Prior Publication Data**

US 2013/0129818 A1 May 23, 2013

3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopflin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	van der Vies
4,093,709 A	6/1978	Choi et al.
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong
4,237,885 A	12/1980	Wong et al.
4,310,510 A	1/1982	Sherman et al.
4,327,725 A	5/1982	Cortese et al.
4,372,951 A	2/1983	Vorys
4,393,871 A	7/1983	Vorhauer et al.
4,402,695 A	9/1983	Wong
4,423,151 A	12/1983	Baranczuk
4,449,980 A	5/1984	Millar et al.
4,610,687 A	9/1986	Fogwell
4,629,449 A	12/1986	Wong
4,732,763 A	3/1988	Beck et al.
4,738,957 A	4/1988	Laurent et al.
4,756,907 A	7/1988	Beck et al.
4,762,717 A	8/1988	Crowley, Jr.
4,788,062 A	11/1988	Gale et al.
4,816,257 A	3/1989	Buster et al.
4,822,616 A	4/1989	Zimmermann et al.
4,865,848 A	9/1989	Cheng et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CN	102258455	11/2011
EP	0275716 A1	7/1988
EP	0622075 A1	11/1994
EP	0785211 A1	1/1996
EP	0785212 A1	1/1996
EP	0811381 A1	6/1997
EP	2191833 A1	6/2010
GB	720561	12/1954
GB	848881 A1	9/1960
GB	874368	8/1961

(Continued)

OTHER PUBLICATIONS

Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547. 2009. Abstract Only.

(Continued)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934	Dolay
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes

Primary Examiner — Frederick Krass*Assistant Examiner* — Dennis J Parad(74) *Attorney, Agent, or Firm* — Marlan D. Walker; Snell & Wilmer LLP(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

6 Claims, 4 Drawing Sheets

US 8,633,178 B2

Page 2

(56)

References Cited**U.S. PATENT DOCUMENTS**

4,900,734 A *	2/1990	Maxson et al.	514/171	6,039,968 A	3/2000	Nabahi
4,906,475 A	3/1990	Kim		6,056,972 A	5/2000	Hermsmeyer
4,942,158 A	7/1990	Sarpotdar et al.		6,060,077 A	5/2000	Meignant
4,961,931 A	10/1990	Wong		6,074,625 A	6/2000	Hawthorne et al.
5,030,629 A	7/1991	Rajadhyaksha		6,077,531 A	6/2000	Salin-Drouin
5,064,654 A	11/1991	Berner et al.		6,080,118 A	6/2000	Blythe
5,108,995 A	4/1992	Casper		6,083,178 A	7/2000	Caillouette
5,128,138 A	7/1992	Blank		6,086,916 A	7/2000	Agnus et al.
5,130,137 A	7/1992	Crowley, Jr.		6,096,338 A	8/2000	Lacy et al.
5,140,021 A	8/1992	Maxson et al.		6,117,446 A	9/2000	Place
5,211,952 A	5/1993	Spicer et al.		6,117,450 A	9/2000	Dittgen et al.
5,252,334 A	10/1993	Chiang et al.		6,133,251 A	10/2000	Dittgen et al.
5,280,023 A	1/1994	Ehrlich et al.		6,133,320 A	10/2000	Yallampalli et al.
5,288,496 A	2/1994	Lewis		6,139,873 A	10/2000	Hughes, Jr. et al.
5,340,584 A	8/1994	Spicer et al.		6,153,216 A	11/2000	Cordes et al.
5,340,585 A	8/1994	Pike et al.		6,165,491 A	12/2000	Grasset et al.
5,340,586 A	8/1994	Pike et al.		6,165,975 A	12/2000	Adams et al.
5,362,497 A	11/1994	Yamada et al.		6,187,339 B1	2/2001	de Haan et al.
5,382,573 A	1/1995	Casper		6,190,331 B1	2/2001	Caillouette
5,393,528 A	2/1995	Staab		6,201,072 B1	3/2001	Rathi et al.
5,393,529 A	2/1995	Hoffmann et al.		6,227,202 B1	5/2001	Matapurkar
5,419,910 A	5/1995	Lewis		6,262,115 B1	7/2001	Guitard et al.
5,468,736 A	11/1995	Hodgen		6,277,418 B1	8/2001	Markaverich et al.
5,474,783 A	12/1995	Miranda et al.		6,283,927 B1	9/2001	Caillouette
5,480,776 A	1/1996	Dullien		6,287,588 B1	9/2001	Shih et al.
5,514,673 A	5/1996	Heckenmuller et al.		6,287,693 B1	9/2001	Savoir et al.
5,516,528 A	5/1996	Hughes et al.		6,294,188 B1	9/2001	Ragavan et al.
5,527,534 A	6/1996	Myhling		6,294,550 B1	9/2001	Place et al.
5,529,782 A	6/1996	Staab		6,299,900 B1	10/2001	Reed et al.
5,543,150 A	8/1996	Bologna et al.		6,306,841 B1	10/2001	Place et al.
5,547,948 A	8/1996	Barcomb		6,306,914 B1	10/2001	de Ziegler et al.
5,565,199 A	10/1996	Page et al.		6,309,669 B1	10/2001	Setterstrom et al.
5,567,831 A	10/1996	Li		6,309,848 B1	10/2001	Howett et al.
5,569,652 A	10/1996	Beier et al.		6,342,491 B1	1/2002	Dey et al.
5,582,592 A	12/1996	Kendrick		6,372,209 B1	4/2002	Chrisope
5,585,370 A	12/1996	Casper		6,387,390 B1	4/2002	Wei et al.
5,595,759 A	1/1997	Wright et al.		6,402,705 B1	6/2002	Deaver et al.
5,595,970 A	1/1997	Garfield et al.		6,416,778 B1	7/2002	Ragavan et al.
5,620,705 A	4/1997	Dong et al.		6,423,039 B1	7/2002	Rathbone et al.
5,629,021 A	5/1997	Wright		6,423,683 B1	7/2002	Heaton et al.
5,633,011 A	5/1997	Dong et al.		6,436,633 B1	8/2002	Kreider et al.
5,633,242 A	5/1997	Oettel et al.		6,440,454 B1	8/2002	Santoro et al.
5,639,743 A	6/1997	Kaswan et al.		6,444,224 B1	9/2002	Rathbone et al.
5,656,286 A	8/1997	Miranda et al.		6,451,339 B2	9/2002	Patel et al.
5,676,968 A	10/1997	Lipp et al.		6,451,779 B1	9/2002	Hesch
5,677,292 A	10/1997	Li et al.		6,455,246 B1	9/2002	Howett et al.
5,694,947 A	12/1997	Lehtinen et al.		6,455,517 B1	9/2002	Tanabe et al.
5,709,844 A	1/1998	Arbeit et al.		6,468,526 B2	10/2002	Chrisope
5,735,801 A	4/1998	Caillouette		6,469,016 B1	10/2002	Place et al.
5,739,176 A	4/1998	Dunn et al.		6,472,434 B1	10/2002	Place et al.
5,744,463 A	4/1998	Bair		6,479,232 B1	11/2002	Howett et al.
5,747,058 A	5/1998	Tipton et al.		6,500,814 B1	12/2002	Hesch
5,770,219 A	6/1998	Chiang et al.		6,503,896 B1	1/2003	Tanabe et al.
5,776,495 A	7/1998	Duclos et al.		6,526,980 B1	3/2003	Tracy et al.
5,788,980 A	8/1998	Nabahi		6,528,094 B1	3/2003	Savoir et al.
5,789,442 A	8/1998	Garfield et al.		6,537,580 B1	3/2003	Savoir et al.
5,811,416 A	9/1998	Chwalisz et al.		6,544,196 B2	4/2003	Caillouette
5,814,329 A	9/1998	Shah		6,544,553 B1	4/2003	Hsia et al.
5,827,200 A	10/1998	Caillouette		6,548,491 B2	4/2003	Tanabe et al.
5,866,603 A	2/1999	Li et al.		6,551,611 B2	4/2003	Elliesen et al.
5,891,868 A	4/1999	Cummings et al.		6,569,463 B2	5/2003	Patel et al.
5,898,038 A	4/1999	Yallampalli et al.		6,583,129 B1	6/2003	Mazer et al.
5,916,176 A	6/1999	Caillouette		6,586,006 B2	7/2003	Roser et al.
RE36,247 E	7/1999	Plunkett et al.		6,589,549 B2	7/2003	Shih et al.
5,922,349 A	7/1999	Elliesen et al.		6,593,317 B1	7/2003	de Ziegler et al.
5,928,666 A	7/1999	Farinas et al.		6,610,652 B2	8/2003	Adams et al.
5,958,446 A	9/1999	Miranda et al.		6,610,670 B2	8/2003	Backensfeld et al.
5,962,445 A	10/1999	Stewart		6,638,536 B2	10/2003	Savoir et al.
5,972,372 A	10/1999	Saleh et al.		6,645,528 B1	11/2003	Straub et al.
5,985,861 A	11/1999	Levine et al.		6,653,298 B2	11/2003	Potter et al.
5,993,856 A	11/1999	Ragavan et al.		6,656,929 B1	12/2003	Agnus et al.
6,001,846 A	12/1999	Edwards et al.		6,660,726 B2	12/2003	Hill et al.
6,022,562 A	2/2000	Autant et al.		6,663,608 B2	12/2003	Rathbone et al.
6,024,976 A	2/2000	Miranda et al.		6,663,895 B2	12/2003	Savoir et al.
6,028,057 A	2/2000	Burns		6,692,763 B1	2/2004	Cummings et al.
				6,737,081 B2	5/2004	Savoir et al.
				6,740,333 B2	5/2004	Beckett et al.
				6,743,815 B2	6/2004	Huebner et al.

US 8,633,178 B2

Page 3

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,747,018 B2	6/2004	Tanabe et al.	7,727,720 B2	6/2010	Dhallan	
6,756,208 B2	6/2004	Griffin et al.	7,732,408 B2	6/2010	Josephson et al.	
6,776,164 B2	8/2004	Bunt et al.	7,749,989 B2	7/2010	Hill et al.	
6,805,877 B2	10/2004	Massara et al.	7,767,656 B2	8/2010	Shoichet et al.	
6,809,085 B1	10/2004	Elson et al.	7,815,949 B2	10/2010	Cohen	
6,818,226 B2	11/2004	Reed et al.	7,829,115 B2	11/2010	Besins et al.	
6,841,716 B1	1/2005	Tsutsumi	RE42,012 E	12/2010	Deaver et al.	
6,844,334 B2	1/2005	Hill et al.	7,858,607 B2	12/2010	Mamchur	
6,855,703 B1	2/2005	Hill et al.	RE42,072 E	1/2011	Deaver et al.	
6,860,859 B2	3/2005	Mehrotra et al.	7,862,552 B2	1/2011	McIntyre et al.	
6,866,865 B2	3/2005	Hsia et al.	7,867,990 B2	1/2011	Schultz et al.	
6,869,969 B2	3/2005	Huebner et al.	7,879,830 B2	2/2011	Wiley	
6,878,518 B2	4/2005	Whitehead	7,884,093 B2	2/2011	Creasy et al.	
6,901,278 B1	5/2005	Notelovitz	7,939,104 B2	5/2011	Barbera et al.	
6,905,705 B2	6/2005	Palm et al.	7,943,602 B2	5/2011	Bunschoten et al.	
6,911,438 B2	6/2005	Wright	7,943,604 B2	5/2011	Coelingh Bennink et al.	
6,923,988 B2	8/2005	Patel et al.	7,989,436 B2	8/2011	Hill et al.	
6,924,274 B2	8/2005	Lardy et al.	7,989,487 B2	8/2011	Welsh et al.	
6,932,983 B1	8/2005	Straub et al.	8,022,053 B2	9/2011	Mueller et al.	
6,939,558 B2	9/2005	Massara et al.	8,048,869 B2	11/2011	Bunschoten et al.	
6,943,021 B2	9/2005	Klausner et al.	8,071,729 B2	12/2011	Giles-Komar et al.	
6,958,327 B1	10/2005	Hillisch et al.	8,076,319 B2	12/2011	Leonard	
6,962,691 B1	11/2005	Lulla et al.	8,088,605 B2	1/2012	Beaudet et al.	
6,962,908 B2	11/2005	Aloba et al.	8,101,209 B2	1/2012	Legrand et al.	
6,967,194 B1	11/2005	Matsuo et al.	8,114,434 B2	2/2012	Sasaki et al.	
6,977,250 B2	12/2005	Rodríguez	8,158,614 B2	4/2012	Lambert et al.	
6,978,945 B2	12/2005	Wong et al.	8,202,736 B2	6/2012	Mousa et al.	
7,005,429 B2	2/2006	Dey et al.	8,217,024 B2	7/2012	Ahmed et al.	
7,011,846 B2	3/2006	Shojaei et al.	8,222,008 B2	7/2012	Thoene	
7,018,992 B2	3/2006	Koch et al.	8,227,454 B2	7/2012	Hill et al.	
7,030,157 B2	4/2006	Ke et al.	8,227,509 B2	7/2012	Castro et al.	
RE39,104 E	5/2006	Duclos et al.	8,241,664 B2	8/2012	Dudley et al.	
7,074,779 B2	7/2006	Sui et al.	8,247,393 B2	8/2012	Ahmed et al.	
7,083,590 B1	8/2006	Bunt et al.	8,273,730 B2	9/2012	Fernandez et al.	
7,091,213 B2	8/2006	Metcalf, III et al.	8,287,888 B2	10/2012	Song et al.	
7,101,342 B1	9/2006	Caillouette	8,329,680 B2	12/2012	Evans et al.	
7,135,190 B2	11/2006	Piao et al.	8,349,820 B2	1/2013	Zeun et al.	
7,163,681 B2	1/2007	Giles-Komar et al.	8,435,561 B2	5/2013	Besins et al.	
7,163,699 B2	1/2007	Besse	2001/005728 A1	6/2001	Guittard et al.	
7,179,799 B2	2/2007	Hill et al.	2001/0021816 A1	9/2001	Caillouette	
7,196,074 B2	3/2007	Blye et al.	2001/0027189 A1	10/2001	Bennink et al.	
7,198,801 B2	4/2007	Carrara et al.	2001/0029357 A1	10/2001	Bunt et al.	
7,226,910 B2	6/2007	Wilson et al.	2001/0031747 A1	10/2001	deZiegler et al.	
7,247,625 B2	7/2007	Zhang et al.	2001/0034340 A1	10/2001	Pickar	
7,250,446 B2	7/2007	Sangita et al.	2001/0056068 A1	12/2001	Chwalisz et al.	
7,300,926 B2	11/2007	Prokai et al.	2002/0012710 A1	1/2002	Lansky	
7,303,763 B2	12/2007	Ho	2002/0026158 A1	2/2002	Rathbone et al.	
7,317,037 B2	1/2008	Fensome et al.	2002/0028788 A1	3/2002	Bunt et al.	
7,329,654 B2	2/2008	Kanojia et al.	2002/0058648 A1	5/2002	Hammerly	
7,335,650 B2	2/2008	Potter et al.	2002/0058926 A1	5/2002	Rathbone et al.	
7,374,779 B2	5/2008	Chen et al.	2002/0076441 A1	6/2002	Shih et al.	
7,378,404 B2	5/2008	Peters et al.	2002/0102308 A1	8/2002	Wei et al.	
7,387,789 B2	6/2008	Klose et al.	2002/0107230 A1	8/2002	Waldon et al.	
7,388,006 B2	6/2008	Schmees et al.	2002/0114803 A1	8/2002	Deaver et al.	
7,414,043 B2	8/2008	Kosemund et al.	2002/0132801 A1	9/2002	Heil et al.	
7,427,413 B2	9/2008	Savoir et al.	2002/0137749 A1	9/2002	Levinson et al.	
7,427,609 B2	9/2008	Leonard	2002/0151530 A1	10/2002	Leonard et al.	
7,429,576 B2	9/2008	Labrie	2002/0156394 A1	10/2002	Mehrotra et al.	
7,431,941 B2	10/2008	Besins et al.	2002/0169150 A1	11/2002	Pickar	
7,459,445 B2	12/2008	Hill et al.	2002/0173510 A1	11/2002	Levinson et al.	
7,465,587 B2	12/2008	Imrich	2002/0193356 A1	12/2002	Van Beek et al.	
7,470,433 B2	12/2008	Carrara et al.	2003/0004145 A1	1/2003	Leonard	
7,485,666 B2	2/2009	Villanueva et al.	2003/007994 A1	1/2003	Bunt et al.	
7,497,855 B2	3/2009	Ausiello et al.	2003/0049307 A1	3/2003	Gyurik	
7,534,765 B2	5/2009	Gregg et al.	2003/0064097 A1	4/2003	Patel et al.	
7,550,142 B2	6/2009	Giles-Komar et al.	2003/0072760 A1	4/2003	Sirbasku	
7,563,565 B1	7/2009	Matsue et al.	2003/0073248 A1	4/2003	Roth et al.	
7,572,779 B2	8/2009	Aloba et al.	2003/0073673 A1	4/2003	Hesch	
7,589,082 B2	9/2009	Savoir et al.	2003/0077297 A1*	4/2003	Chen et al. 424/400	
7,671,027 B2	3/2010	Loumaye	2003/0091640 A1	5/2003	Ramanathan et al.	
7,674,783 B2	3/2010	Hermsmeyer	2003/0092691 A1	5/2003	Besse et al.	
7,687,281 B2	3/2010	Roth et al.	2003/0096012 A1	5/2003	Besse et al.	
7,687,485 B2	3/2010	Levinson et al.	2003/0104048 A1	6/2003	Patel et al.	
7,694,683 B2	4/2010	Callister et al.	2003/0114420 A1	6/2003	Salvati et al.	
7,704,983 B1	4/2010	Hodgen et al.	2003/0124182 A1	7/2003	Shojaei et al.	
			2003/0124191 A1	7/2003	Besse et al.	
			2003/0130558 A1	7/2003	Massara et al.	
			2003/0144258 A1	7/2003	Heil et al.	

US 8,633,178 B2

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(56)

References Cited**U.S. PATENT DOCUMENTS**

2003/0157157 A1	8/2003	Luo et al.	2006/0020002 A1	1/2006	Salvati et al.
2003/0166509 A1	9/2003	Edwards et al.	2006/0030615 A1	2/2006	Fensome et al.
2003/0180352 A1	9/2003	Patel et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2003/0181353 A1	9/2003	Nyce	2006/0052341 A1	3/2006	Cornish et al.
2003/0181728 A1	9/2003	Salvati et al.	2006/0069031 A1	3/2006	Loumaye
2003/0191096 A1	10/2003	Leonard et al.	2006/0083778 A1	4/2006	Allison et al.
2003/0195177 A1	10/2003	Leonard et al.	2006/0089337 A1	4/2006	Casper et al.
2003/0215496 A1	11/2003	Patel et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2003/0220297 A1	11/2003	Berstein et al.	2006/0106004 A1	5/2006	Brody et al.
2003/0224057 A1	12/2003	Martin-Letellier et al.	2006/0111424 A1	5/2006	Salvati et al.
2003/0224059 A1	12/2003	Lerner et al.	2006/0121626 A1	6/2006	Imrich
2003/0225050 A1 *	12/2003	Grawe et al. 514/179	2006/0135619 A1	6/2006	Kick et al.
2003/0228686 A1	12/2003	Klausner et al.	2006/0194775 A1	8/2006	Tofovic et al.
2003/0229057 A1	12/2003	Caubel et al.	2006/0204557 A1	9/2006	Gupta et al.
2004/0009960 A1	1/2004	Heil et al.	2006/0235037 A1	10/2006	Purandare et al.
2004/0034001 A1	2/2004	Karara	2006/0240111 A1	10/2006	Fernandez et al.
2004/0037881 A1	2/2004	Guittard et al.	2006/0247216 A1	11/2006	Haj-Yehia
2004/0043943 A1	3/2004	Guittard et al.	2006/0252049 A1	11/2006	Shuler et al.
2004/0044080 A1	3/2004	Place et al.	2006/0257472 A1	11/2006	Nielsen
2004/0073024 A1	4/2004	Metcalf, III et al.	2006/0275360 A1	12/2006	Ahmed et al.
2004/0077605 A1	4/2004	Salvati et al.	2006/0280771 A1	12/2006	Groenewegen et al.
2004/0077606 A1	4/2004	Salvati et al.	2006/0280797 A1	12/2006	Shoichet et al.
2004/0087548 A1	5/2004	Salvati et al.	2006/0280800 A1	12/2006	Nagi et al.
2004/0089308 A1	5/2004	Welch	2007/0004693 A1	1/2007	Woolfson et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2007/0004694 A1	1/2007	Woolfson et al.
2004/0097468 A1	5/2004	Wimalawansa	2007/0021360 A1	1/2007	Nyce et al.
2004/0101557 A1	5/2004	Gibson et al.	2007/0027201 A1	2/2007	McComas et al.
2004/0106542 A1	6/2004	Deaver et al.	2007/0031491 A1	2/2007	Levine et al.
2004/0131670 A1	7/2004	Gao	2007/0042038 A1	2/2007	Besse
2004/0142012 A1	7/2004	Bunt et al.	2007/0066628 A1	3/2007	Zhang et al.
2004/0146894 A1	7/2004	Warrington et al.	2007/0066637 A1	3/2007	Zhang et al.
2004/0176324 A1	9/2004	Salvati et al.	2007/0066675 A1	3/2007	Zhang et al.
2004/0176336 A1	9/2004	Rodriguez	2007/0093548 A1	4/2007	Diffendal et al.
2004/0185104 A1	9/2004	Piao et al.	2007/0116729 A1	5/2007	Palepu
2004/0191276 A1	9/2004	Muni	2007/0116829 A1	5/2007	Prakash et al.
2004/0198706 A1	10/2004	Carrara et al.	2007/0178166 A1	8/2007	Bernstein et al.
2004/0213744 A1	10/2004	Lulla et al.	2007/0184558 A1	8/2007	Roth et al.
2004/0234606 A1	11/2004	Levine et al.	2007/0191319 A1	8/2007	Ke et al.
2004/0255319 A1	12/2004	Netke et al.	2007/0196433 A1	8/2007	Ron et al.
2004/0259817 A1	12/2004	Waldon et al.	2007/0207225 A1	9/2007	Squadrito
2004/0266745 A1	12/2004	Schwanitz et al.	2007/0225281 A1	9/2007	Zhang et al.
2005/0004088 A1	1/2005	Hesch	2007/0238713 A1	10/2007	Gast et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2007/0243229 A1	10/2007	Smith et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2007/0264309 A1	11/2007	Chollet et al.
2005/0021009 A1	1/2005	Massara et al.	2007/0264345 A1	11/2007	Eros et al.
2005/0025833 A1	2/2005	Aschkenasy et al.	2007/0286819 A1	12/2007	DeVries et al.
2005/0031651 A1	2/2005	Gervais et al.	2007/0292387 A1	12/2007	Jon et al.
2005/0042173 A1	2/2005	Besse et al.	2008/0026035 A1	1/2008	Chollet et al.
2005/0048116 A1	3/2005	Straub et al.	2008/0026062 A1	1/2008	Farr et al.
2005/0079138 A1	4/2005	Chickering, III et al.	2008/0038350 A1	2/2008	Gerecke et al.
2005/0085453 A1	4/2005	Govindarajan	2008/0085877 A1	4/2008	Bortz
2005/0101579 A1	5/2005	Shippen	2008/0095838 A1	4/2008	Abou Chakra-Vernet
2005/0113350 A1	5/2005	Duesterberg et al.	2008/0113953 A1	5/2008	De Vries et al.
2005/0118272 A1	6/2005	Besse et al.	2008/0114050 A1	5/2008	Fensome et al.
2005/0153946 A1	7/2005	Hirsh et al.	2008/0119537 A1	5/2008	Zhang et al.
2005/0164977 A1	7/2005	Coelingh Bennink	2008/0125402 A1	5/2008	Diliberti
2005/0182105 A1	8/2005	Nirschl et al.	2008/0138379 A1	6/2008	Jennings-Spring
2005/0187267 A1	8/2005	Hamann et al.	2008/0145423 A1	6/2008	Khan et al.
2005/0192253 A1	9/2005	Salvati et al.	2008/0188829 A1	8/2008	Creasy
2005/0192310 A1	9/2005	Gavai et al.	2008/0206161 A1	8/2008	Tamarkin et al.
2005/0207990 A1	9/2005	Funke et al.	2008/0220069 A1	9/2008	Allison
2005/0214384 A1	9/2005	Juturu et al.	2008/0234199 A1	9/2008	Katamreddy
2005/0220825 A1	10/2005	Funke et al.	2008/0255078 A1	10/2008	Katamreddy
2005/0222106 A1	10/2005	Bracht	2008/0255089 A1	10/2008	Katamreddy
2005/0244522 A1	11/2005	Carrara et al.	2008/0299220 A1	12/2008	Tamarkin et al.
2005/0245902 A1	11/2005	Cornish et al.	2008/0312197 A1	12/2008	Rodriguez
2005/0250746 A1	11/2005	Iammatteo	2008/0312198 A1	12/2008	Rodriguez
2005/0250750 A1	11/2005	Cummings et al.	2009/0060982 A1	3/2009	Ron et al.
2005/0250753 A1	11/2005	Fink et al.	2009/0068118 A1	3/2009	Eini et al.
2005/0256028 A1	11/2005	Yun et al.	2009/0081278 A1	3/2009	De Graaff et al.
2005/0266078 A1	12/2005	Jorda et al.	2009/0081303 A1	3/2009	Savoir et al.
2005/0272712 A1	12/2005	Grubb et al.	2009/0092656 A1	4/2009	Klamerus et al.
2006/0014728 A1	1/2006	Chwalisz et al.	2009/0099106 A1	4/2009	Phiasivongsa et al.
2006/0018937 A1	1/2006	Friedman et al.	2009/0131385 A1	5/2009	Voskuhl
2006/0019978 A1	1/2006	Balog	2009/0137478 A1	5/2009	Bernstein et al.
			2009/0137538 A1	5/2009	Klamerus et al.
			2009/0143344 A1	6/2009	Chang
			2009/018088 A1	7/2009	Song et al.
			2009/0214474 A1	8/2009	Jennings

US 8,633,178 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2009/0227025 A1	9/2009	Nichols et al.	WO	9630000	A1	10/1996
2009/0232897 A1	9/2009	Sahoo et al.	WO	9743989	A1	11/1997
2009/0258096 A1	10/2009	Cohen	WO	9810293	A1	3/1998
2009/0264395 A1	10/2009	Creasy	WO	9832465	A1	7/1998
2009/0269403 A1	10/2009	Shaked et al.	WO	9851280	A1	11/1998
2009/0285772 A1	11/2009	Phasivongsa et al.	WO	9939700	A1	2/1999
2009/0325916 A1	12/2009	Zhang et al.	WO	9932072	A1	7/1999
2010/0028360 A1	2/2010	Atwood	WO	9942109	A1	8/1999
2010/0040671 A1	2/2010	Ahmed et al.	WO	9948477	A1	9/1999
2010/0048523 A1	2/2010	Bachman et al.	WO	9553910	A2	10/1999
2010/0074959 A1	3/2010	Hansom et al.	WO	0038659	A1	11/1999
2010/0086599 A1	4/2010	Huempel et al.	WO	9963974	A2	12/1999
2010/0092568 A1	4/2010	Lerner et al.	WO	0006175	A1	2/2000
2010/0105071 A1	4/2010	Laufer et al.	WO	0045795	A2	8/2000
2010/0129320 A1	5/2010	Phasivongsa et al.	WO	0050007	A1	8/2000
2010/0136105 A1	6/2010	Chen et al.	WO	0059577	A1	10/2000
2010/0137265 A1	6/2010	Leonard	WO	0137808	A1	11/2000
2010/0137271 A1	6/2010	Chen et al.	WO	0076522	A1	12/2000
2010/0152144 A1	6/2010	Hermsmeyer	WO	0154699	A1	8/2001
2010/0168228 A1	7/2010	Bose et al.	WO	0160325	A1	8/2001
2010/0183723 A1	7/2010	Laurent-Applegate et al.	WO	0207700	A2	1/2002
2010/0184736 A1	7/2010	Coelingh Bennink et al.	WO	0211768	A1	2/2002
2010/0190758 A1	7/2010	Fauser et al.	WO	0222132	A2	3/2002
2010/0240626 A1	9/2010	Kulkarni et al.	WO	0240008	A2	5/2002
2010/0255085 A1	10/2010	Liu et al.	WO	02053131	A1	7/2002
2010/0303825 A9	12/2010	Sirbasku	WO	03041718	A1	5/2003
2010/0312137 A1	12/2010	Gilmour et al.	WO	03041741	A1	5/2003
2010/0316724 A1	12/2010	Whitfield et al.	WO	03068186	A1	8/2003
2010/0330168 A1	12/2010	Gicquel et al.	WO	03082254	A1	10/2003
2011/0028439 A1	2/2011	Witt-Enderby et al.	WO	03092588	A2	11/2003
2011/0053845 A1	3/2011	Levine et al.	WO	2004017983	A1	3/2004
2011/0076775 A1	3/2011	Stewart et al.	WO	2005027911	A1	3/2004
2011/0076776 A1	3/2011	Stewart et al.	WO	2004032897	A2	4/2004
2011/0086825 A1	4/2011	Chatroux	WO	2004052336	A2	6/2004
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	WO	2005120517	A1	6/2004
2011/0098631 A1	4/2011	McIntyre et al.	WO	2004054540	A2	7/2004
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	WO	2004080413	A2	9/2004
2011/0135719 A1	6/2011	Besins et al.	WO	2005030175	A1	4/2005
2011/0182997 A1	7/2011	Lewis et al.	WO	2005087194	A1	9/2005
2011/0195114 A1	8/2011	Carrara et al.	WO	2005087199	A2	9/2005
2011/0195944 A1	8/2011	Mura et al.	WO	2005105059	A1	11/2005
2011/0217341 A1	9/2011	Sah	WO	2005115335	A1	12/2005
2011/0250274 A1	10/2011	Shaked et al.	WO	2005120470	A1	12/2005
2011/0256092 A1	10/2011	Phasivongsa et al.	WO	20060113369	A2	2/2006
2011/0262494 A1	10/2011	Achleitner et al.	WO	2006034090	A1	3/2006
2011/0268665 A1	11/2011	Tamarkin et al.	WO	2006036899	A2	4/2006
2011/0293720 A1	12/2011	General et al.	WO	2006053172	A2	5/2006
2011/0311592 A1	12/2011	Birbara	WO	2006105615	A1	10/2006
2011/0312927 A1	12/2011	Nachaegari et al.	WO	2006113505	A2	10/2006
2011/0312928 A1	12/2011	Nachaegari et al.	WO	2006138686	A1	12/2006
2012/0009276 A1	1/2012	De Groot	WO	2006138735	A2	12/2006
2012/0015350 A1	1/2012	Nabatianyan et al.	WO	2007045027	A1	4/2007
2012/0045532 A1	2/2012	Cohen	WO	2007103294	A2	9/2007
2012/0052077 A1	3/2012	Truitt, III et al.	WO	2007123790	A1	11/2007
2012/0128625 A1	5/2012	Shalwitz et al.	WO	2007124250	A2	11/2007
2012/0128777 A1	5/2012	Keck et al.	WO	2007144151	A1	12/2007
2012/0149748 A1	6/2012	Shanler et al.	WO	2008049516	A3	5/2008
2012/0269721 A1	10/2012	Weng et al.	WO	2008152444	A2	12/2008
2012/0269878 A2	10/2012	Cantor et al.	WO	2009002542	A1	12/2008
2012/0283671 A1	11/2012	Shibata et al.	WO	2009036311	A1	3/2009
2013/0022674 A1	1/2013	Dudley et al.	WO	2009069006	A2	6/2009
2013/0029947 A1	1/2013	Nachaegari et al.	WO	2009098072	A2	8/2009
2013/0129818 A1	5/2013	Bernick et al.	WO	2009133352	A2	11/2009

FOREIGN PATENT DOCUMENTS

IN	216026	3/2008
IN	2005KO00053	9/2009
IN	244217	11/2010
WO	9011064 A1	10/1990
WO	9317686 A1	9/1993
WO	9422426 A1	3/1994
WO	9530409 A1	11/1995
WO	9609826 A2	4/1996

OTHER PUBLICATIONS

Azure Pharma, Inc., "Elestrin™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, 2009.
 Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, 2005.

US 8,633,178 B2

Page 6

(56)

References Cited

OTHER PUBLICATIONS

- Committee of Obstetric Practice, Committee Opinion—No. 522, *Obstetrics & Gynecology*, 119(4):879-882, 2012.
- Diramio, “Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs,” The University of Georgia—Masters of Science Thesis, 131 pages, 2004. http://athenaearm.lib.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1.
- Ganem-Qintanar et al., “Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss,” *International Journal of Pharmaceutics*, 147(2):165-171, 1997. Abstract Only.
- Johanson, “Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester,” *Critical Reviews in Toxicology*, 30(3):307-345, 2000. Abstract Only.
- Knuth et al., “Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations,” *Advanced Drug Delivery Reviews*, 11(1-2):137-167, 1993. Abstract Only.
- Lucy et al., “Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle,” *Biol Reprod.*, 35(2):300-11, 1986. Abstract Only.
- NuGen, “What is NuGen HP Hair Growth System?” <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, 3 pages, undated.
- NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, 4 pages, undated.
- Panchagnula et al., “Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies,” *J Pharm Pharmacol.*, 43(9):609-14, 1991. Abstract Only.
- Salole, “The physicochemical properties of oestradiol,” *Journal of Pharmaceutical & Biomedical Analysis*, 5(7):635-648, 1987.
- Strickley, “Solubilizing Excipients in Oral and Injectable Formulations,” *Pharmaceutical Research*, 21(2):201-230, 2004.
- Tahition Noni, “Body Balance Cream,” http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/, 1 page, undated.
- Trommer et al., “Overcoming the Stratum Corneum: The Modulation of Skin Penetration,” *Skin Pharmacol Physiol.*, 19:106-121, 2006. http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf.
- International Search report for corresponding International Application No. PCT/US12/66406, mailed Jan. 24, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/023309 mailed Apr. 9, 2013.
- Acarturk, “Mucoadhesive Vaginal Drug Delivery System,” *Recent Patents on Drug Delivery & Formulation*, 3 (3):193-205, 2009.
- Fuchs et al., “The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study,” *Aesthetic Dermatology*, 8(1):14-19, 2006.
- Panay et al., “The 2013 British Menopause Society & Women’s Health Concern recommendations on hormone replacement therapy,” DOI: 0.1177/1754045313489645, [min.sagepub.com](http://journals.sagepub.com). *Menopause International: The Integrated Journal of Postreproductive Health* 0(0):1-10, 2013.
- Bhavnani et al., “Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy,” *J Clin Endocrinol Metab.* doi:10.1210/jc.2011-2492, 97(3):0000-0000, 2011, 4 pages.
- Bhavnani et al., “Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER α and ER β ,” *Endocrinology* 2008;149(10):4857-4870.
- Du et al., “Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood,” *Menopause: The Journal of the North American Menopause Society*, doi: 10.1097/gme.0b013e31828d39a2, 20(11):0000-0000, 2013, 7 pages.
- Hargrove et al., “Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronize Estradiol and Progesterone,” *Obstetrics & Gynecology: Estrogen Replacement Therapy* 1989;73(4):606-612.
- Patel et al., “Transdermal Drug Delivery System: A Review,” *The Pharma Innovation* 2012;1(4):78-87.
- Sarrel et al., “The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years,” *American Journal of Public Health, Research and Practice*, e1-e6. doi:10.2105/AJPH.2013.301295, 2013.
- Sitruk-Ware, “Progestogens in hormonal replacement therapy: new molecules, risks, and benefits,” *Menopause: The Journal of the North American Menopause Society* 2002;9(1):6-15.
- Stanczyk et al., “Ethynodiol and 17 β -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment,” *Elsevier* 2013;87:706-727.
- Wood et al., “Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys,” *Breast Cancer Res Treat* 2007;101:125-134.
- Fotherby, “Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy,” *Elsevier* 1996;54:59-69.
- Kincl et al., “Increasing Oral Bioavailability of Progesterone by Formulation,” *Journal of Steroid Biochemistry* 1978;9:83-84.
- NAMS “Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society,” *Menopause: The Journal of the North American Menopause Society* 2013;20(9):888-902.
- Sitruk-Ware et al., “Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review,” *Contraception* 1987;36(4):373-402.
- Shufelt et al., “Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women’s Health Initiative Observational Study,” *Menopause: The Journal of the North American Menopause Society* 2013;DOI: 10.1097/GME.0b013e31829a64f9:1-7.
- Smith et al., “Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens,” *JAMA Internal Medicine* 2013;doi:10.1001/jamainternmed.2013.11074:E1-E7.
- Whitehead et al., “Absorption and metabolism of oral progesterone,” *British Medical Journal* 1980:825-827.
- US 6,214,374, 04/2001, Schmirler et al. (withdrawn)

* cited by examiner

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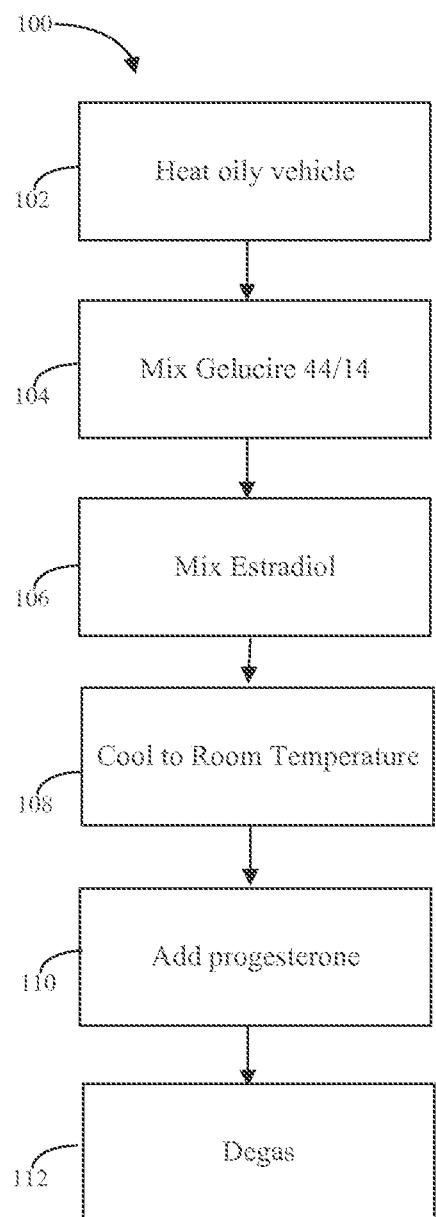
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Fig. 1

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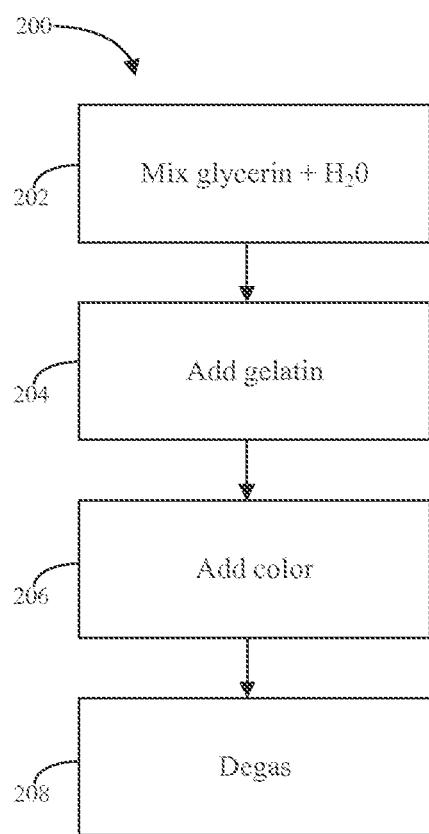


Fig. 2

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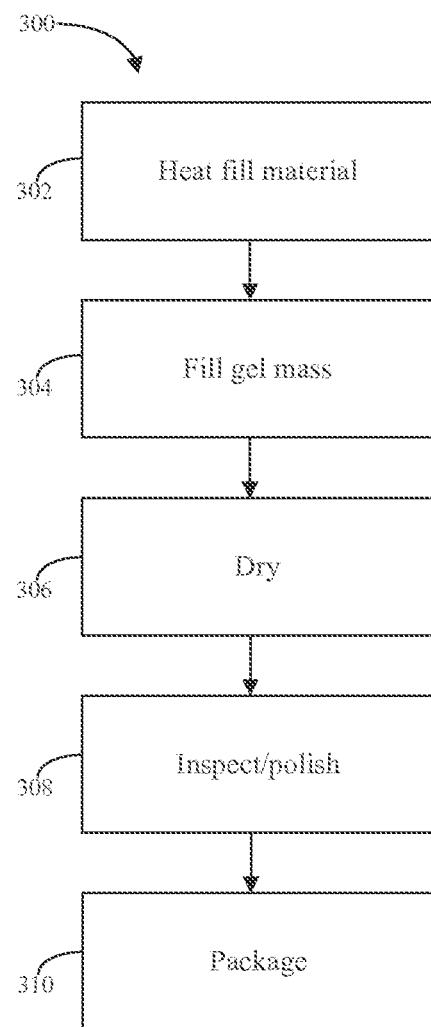


Fig. 3

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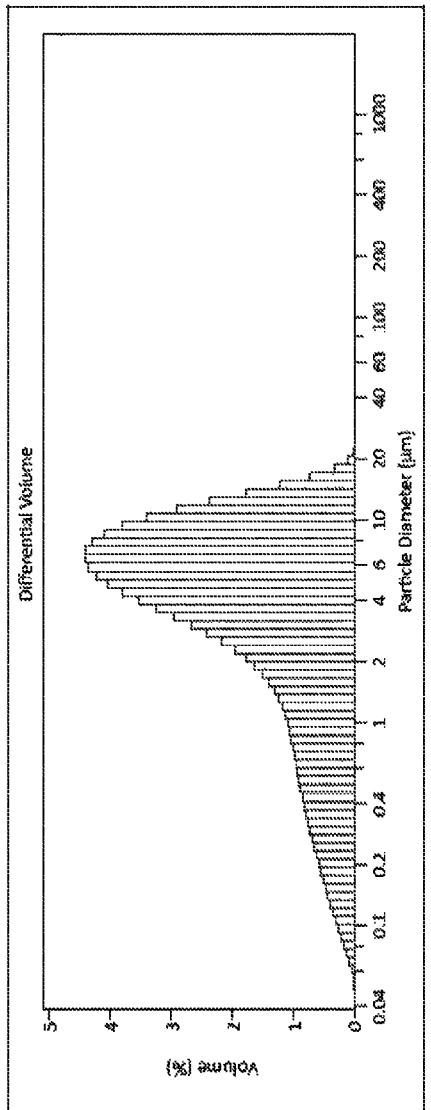


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a nonprovisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563, 408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and 3. U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREMPRO (conjugated estrogens/methoxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus methoxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic methoxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

**BRIEF DESCRIPTION OF THE
DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

**DETAILED DESCRIPTION OF THE
ILLUSTRATED EMBODIMENTS**

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

DEFINITIONS

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of

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progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

5 These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

10 Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

15 Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction 20 Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

25 The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm . The ULM is a liquid based 30 module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may 35 be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other 40 suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the 45 Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. 50 Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

55 The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may 60 use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These 65 formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progest-

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erone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

5 In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

10 In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

15 In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glycercyl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

20 Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

25 In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

30 In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

35 In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

40 For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

45 The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may 50 comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

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As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the com-

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monly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference—Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol nonoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol nonoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
polysorbate 80: CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride): CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethyl-

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ene glycol monoethyl ether):MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride)	12	Clear, after 12 days
CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether)	12	Clear, after 12 days
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	12	Clear, after 12 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear, after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether):	12	Hazy
MIGLYOL 812 (Caprylic/Capric Triglyceride):		
CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear
CAPMUL MCM(Medium Chain Mono- and Diglycerides)		
TRANSCUTOL (Diethylene glycol monoethyl ether)	12	Hazy
MIGLYOL 812 (Caprylic/Capric Triglyceride):		
CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)		

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethyl ether (TRANSCUTOL HP) (Highly purified diethylene glycol monoethyl ether EP/NF)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

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In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	322.97	99.38	3.23 kg
Total	100	3.25 kg	

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

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TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):	86.4
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) (9:1)	
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	70.5
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) (7:3)	
CAPMUL MCM (Medium Chain Mono- and Diglycerides):	57.4
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF	82.57	577.97	
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF	10.0	70.00	
TOTAL	100.00		700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this

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Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C./+2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 Caprylic/Capric Triglyceride) or equivalent	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) MIGLYOL is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00	mg 100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride	65.93	428.55	Carrier
MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)			
Lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) or equivalent)	300	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API com-

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prising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF	82.57	577.97	5.78	
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF	10.0	70.00	0.70	
	Total:	100.00	700.00	7.00	

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

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Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
Total:		100.000		200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
Total:		100.00		600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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Example 15

Progesterone and Estradiol Combination Study
Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

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All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C.±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any

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suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+-10° C. The wedge temperature may be 38° C.+-3° C. The drum cooling temperature may be 4° C.+-2° C. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical formulation comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent;
 - wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;
 - wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and
 - wherein the solubilizing agent comprises a C6-C12 oil.
2. The pharmaceutical formulation of claim 1, further comprising partially solubilized progesterone.

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3. The pharmaceutical formulation of claim 1, wherein the formulation is contained within a gelatin capsule.

4. The pharmaceutical formulation of claim 1, wherein the medium chain solubilizing agent is selected from at least one of mono-, di-, and triglycerides and combinations thereof. 5

5. The pharmaceutical formulation of claim 1, wherein said estrogen has a dosage strength at least about 0.125 mg and wherein said progesterone has a dosage strength at least about 25 mg.

6. The pharmaceutical formulation of claim 1, wherein the 10 ratio of progesterone to estradiol is at least 95:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,633,178 B2
APPLICATION NO. : 13/684002
DATED : January 21, 2014
INVENTOR(S) : Brian A. Bernick et al.

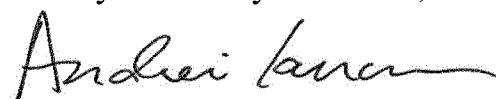
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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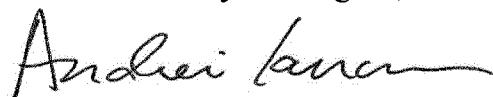
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 23, Claim 5, Line 7: Delete “estrogen” and insert in its place --estradiol--.

Signed and Sealed this
Twentieth Day of August, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT B



US008846648B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 8,846,648 B2
(45) **Date of Patent:** *Sep. 30, 2014

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Neda Irani**, Palm Beach Garden, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)

(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/099,545**

(22) Filed: **Dec. 6, 2013**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**

A01N 45/00 (2006.01)
A61K 9/48 (2006.01)
A61K 31/565 (2006.01)
A61K 9/16 (2006.01)
A61K 31/57 (2006.01)

(52) **U.S. Cl.**

CPC *A61K 31/57* (2013.01); *A61K 9/4858* (2013.01); *A61K 31/565* (2013.01); *A61K 9/16* (2013.01)

USPC **514/169**; 424/452

(58) **Field of Classification Search**

USPC 514/169
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934	Doisy
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Grant et al.
3,198,707 A	8/1965	Nomaine et al.
3,478,070 A	11/1969	Smith et al.
3,526,648 A	9/1970	Bertin et al.

3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Higuchi et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes
4,012,496 A	3/1977	Hartmann et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	Van Der Vies
4,093,709 A	6/1978	Choi
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong
4,237,885 A	12/1980	Wong
4,310,510 A	1/1982	Sherman et al.
4,327,725 A	5/1982	Cortese et al.
4,372,951 A	2/1983	Vorys
4,384,096 A	5/1983	Sonnabend

(Continued)

FOREIGN PATENT DOCUMENTS

CN	102258455 A	11/2011
EP	0275716 A1	7/1988
EP	0622075 A1	11/1994
EP	0785211 A1	1/1996
EP	0811381 A1	6/1997

(Continued)

OTHER PUBLICATIONS

Chempro, "Fatty Acid Composition of Some Major Oils," available at <http://www.chempro.in/fattyacid.htm>, webpage captured on May 26, 2010 (2 total pages).*

(Continued)

Primary Examiner — Frederick Krass

Assistant Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP; Marian D. Walker

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

US 8,846,648 B2

Page 2

(56)	References Cited						
U.S. PATENT DOCUMENTS							
4,393,871 A	7/1983	Vorhauer	5,827,200 A	10/1998	Caillouette		
4,402,695 A	9/1983	Wong	5,866,603 A	2/1999	Li et al.		
4,423,151 A	12/1983	Baranczuk	5,891,868 A	4/1999	Cummings et al.		
4,449,980 A	5/1984	Millar et al.	5,898,038 A	4/1999	Yallampalli et al.		
4,610,687 A	9/1986	Fogwell	5,916,176 A	6/1999	Caillouette		
4,629,449 A	12/1986	Wong	RE36,247 E	7/1999	Plunkett et al.		
4,732,763 A	3/1988	Beck et al.	5,922,349 A	7/1999	Elliesen et al.		
4,738,957 A	4/1988	Laurent et al.	5,928,666 A	7/1999	Farinas et al.		
4,756,907 A	7/1988	Beck et al.	5,958,446 A	9/1999	Miranda et al.		
4,762,717 A	8/1988	Crowley	5,962,445 A	10/1999	Stewart		
4,788,062 A	11/1988	Gale et al.	5,972,372 A	10/1999	Saleh et al.		
4,816,257 A	3/1989	Buster et al.	5,985,861 A	11/1999	Levine et al.		
4,822,616 A	4/1989	Zimmermann et al.	5,993,856 A	11/1999	Ragavan et al.		
4,865,848 A	9/1989	Cheng et al.	6,001,846 A	12/1999	Edwards et al.		
4,900,734 A *	2/1990	Maxson et al.	514/171	6,022,562 A	2/2000	Autant et al.	
4,906,475 A	3/1990	Kim	6,024,976 A	2/2000	Miranda et al.		
4,942,158 A	7/1990	Sarpotdar et al.	6,028,057 A	2/2000	Burns		
4,961,931 A	10/1990	Wong	6,039,968 A	3/2000	Nabahi		
5,030,629 A	7/1991	Rajadhyaksha	6,056,972 A	5/2000	Hermsmeyer		
5,064,654 A	11/1991	Berner et al.	6,060,077 A	5/2000	Meignant		
5,108,995 A	4/1992	Casper	6,074,625 A	6/2000	Hawthorne et al.		
5,128,138 A	7/1992	Blank	6,077,531 A	6/2000	Salin-Drouin		
5,130,137 A	7/1992	Crowley	6,080,118 A	6/2000	Blythe		
5,140,021 A	8/1992	Maxson et al.	6,083,178 A	7/2000	Caillouette		
5,211,952 A	5/1993	Pike et al.	6,086,916 A	7/2000	Agnus et al.		
5,252,334 A	10/1993	Chiang et al.	6,096,338 A	8/2000	Lacy et al.		
5,280,023 A	1/1994	Ehrlich et al.	6,117,446 A	9/2000	Place		
5,288,496 A	2/1994	Lewis	6,117,450 A	9/2000	Dittgen et al.		
5,340,584 A	8/1994	Spicer et al.	6,133,251 A	10/2000	Dittgen et al.		
5,340,585 A	8/1994	Pike et al.	6,133,320 A	10/2000	Yallampalli et al.		
5,340,586 A	8/1994	Pike et al.	6,139,873 A	10/2000	Hughes, Jr. et al.		
5,362,497 A	11/1994	Yamada et al.	6,153,216 A	11/2000	Cordes et al.		
5,382,573 A	1/1995	Casper	6,165,491 A	12/2000	Grasset et al.		
5,393,528 A	2/1995	Staab	6,165,975 A	12/2000	Adams et al.		
5,393,529 A	2/1995	Hoffmann et al.	6,187,339 B1	2/2001	de Haan et al.		
5,419,910 A	5/1995	Lewis	6,190,331 B1	2/2001	Caillouette		
5,468,736 A	11/1995	Hodgen	6,201,072 B1	3/2001	Rathi et al.		
5,474,783 A	12/1995	Miranda et al.	6,227,202 B1	5/2001	Matapurkar		
5,480,776 A	1/1996	Dullien	6,262,115 B1	7/2001	Guitard et al.		
5,514,673 A	5/1996	Heckenmuller et al.	6,277,418 B1	8/2001	Markaverich et al.		
5,516,528 A	5/1996	Hughes et al.	6,283,927 B1	9/2001	Caillouette		
5,527,534 A	6/1996	Myhling	6,287,588 B1	9/2001	Shih et al.		
5,529,782 A	6/1996	Staab	6,287,693 B1	9/2001	Savoir et al.		
5,543,150 A	8/1996	Bologna et al.	6,294,188 B1	9/2001	Ragavan et al.		
5,547,948 A	8/1996	Barcomb	6,294,192 B1	9/2001	Patel et al.		
5,565,199 A	10/1996	Page et al.	6,294,550 B1	9/2001	Place et al.		
5,567,831 A	10/1996	Li	6,299,900 B1	10/2001	Reed et al.		
5,569,652 A	10/1996	Beier et al.	6,306,841 B1	10/2001	Place et al.		
5,582,592 A	12/1996	Kendrick	6,306,914 B1	10/2001	Ziegler et al.		
5,585,370 A	12/1996	Casper	6,309,669 B1	10/2001	Setterstrom et al.		
5,595,759 A	1/1997	Wright et al.	6,309,848 B1	10/2001	Howett et al.		
5,595,970 A	1/1997	Garfield et al.	6,342,491 B1	1/2002	Dey et al.		
5,620,705 A	4/1997	Dong et al.	6,372,209 B1	4/2002	Chrisope		
5,629,021 A	5/1997	Wright	6,372,246 B1	4/2002	Wei et al.		
5,633,011 A	5/1997	Dong et al.	6,387,390 B1	5/2002	Deaver et al.		
5,633,242 A	5/1997	Oettel et al.	6,402,705 B1	6/2002	Caillouette		
5,639,743 A	6/1997	Kaswan et al.	6,416,778 B1	7/2002	Ragavan et al.		
5,656,286 A	8/1997	Miranda et al.	6,423,039 B1	7/2002	Rathbone et al.		
5,676,968 A	10/1997	Lipp et al.	6,423,683 B1	7/2002	Heaton et al.		
5,677,292 A	10/1997	Li et al.	6,436,633 B1	8/2002	Kreider et al.		
5,694,947 A	12/1997	Lehtinen et al.	6,440,454 B1	8/2002	Santoro et al.		
5,709,844 A	1/1998	Arbeit et al.	6,444,224 B1	9/2002	Rathbone et al.		
5,735,801 A	4/1998	Caillouette	6,444,234 B1	9/2002	Kirby et al.		
5,739,176 A	4/1998	Dunn et al.	6,451,339 B2	9/2002	Patel et al.		
5,744,463 A	4/1998	Bair	6,451,779 B1	9/2002	Hesch		
5,747,058 A	5/1998	Tipton et al.	6,455,246 B1	9/2002	Howett et al.		
5,762,614 A	6/1998	Caillouette	6,455,517 B1	9/2002	Tanabe et al.		
5,770,176 A	6/1998	Nargessi	6,468,526 B2	10/2002	Chrisope		
5,770,219 A	6/1998	Chiang et al.	6,469,016 B1	10/2002	Place et al.		
5,776,495 A	7/1998	Duclos et al.	6,472,434 B1	10/2002	Place et al.		
5,788,980 A	8/1998	Nabahi	6,479,232 B1	11/2002	Howett et al.		
5,789,442 A	8/1998	Garfield et al.	6,500,814 B1	12/2002	Hesch		
5,811,416 A	9/1998	Chwalisz et al.	6,503,896 B1	1/2003	Tanabe et al.		
5,811,547 A	9/1998	Nakamichi et al.	6,511,969 B1	1/2003	Hermsmeyer		
5,814,329 A	9/1998	Shah	6,526,980 B1	3/2003	Tracy et al.		
			6,528,094 B1	3/2003	Savoir et al.		
			6,537,580 B1	3/2003	Savoir et al.		
			6,544,196 B2	4/2003	Caillouette		
			6,544,553 B1	4/2003	Hsia et al.		

US 8,846,648 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

6,548,491 B2	4/2003	Tanabe et al.	7,388,006 B2	6/2008	Schmees et al.
6,551,611 B2	4/2003	Elliesen et al.	7,414,043 B2	8/2008	Kosemund et al.
6,569,463 B2	5/2003	Patel et al.	7,427,413 B2	9/2008	Savoir et al.
6,583,129 B1	6/2003	Mazer et al.	7,427,609 B2	9/2008	Leonard
6,586,006 B2	7/2003	Roser et al.	7,429,576 B2	9/2008	Labrie
6,589,549 B2	7/2003	Shih et al.	7,431,941 B2	10/2008	Besins et al.
6,593,317 B1	7/2003	de Ziegler et al.	7,459,445 B2	12/2008	Hill et al.
6,610,652 B2	8/2003	Adams et al.	7,465,587 B2	12/2008	Imrich
6,610,670 B2	8/2003	Backensfeld et al.	7,470,433 B2	12/2008	Carrara et al.
6,638,536 B2	10/2003	Savoir et al.	7,485,666 B2	2/2009	Villanueva et al.
6,645,528 B1	11/2003	Straub et al.	7,497,855 B2	3/2009	Ausiello et al.
6,653,298 B2	11/2003	Potter et al.	7,534,765 B2	5/2009	Gregg et al.
6,656,929 B1	12/2003	Agnus et al.	7,550,142 B2	6/2009	Giles-Komar et al.
6,660,726 B2	12/2003	Hill et al.	7,563,565 B1	7/2009	Matsuo et al.
6,663,608 B2	12/2003	Rathbone et al.	7,572,779 B2	8/2009	Aloba et al.
6,663,895 B2	12/2003	Savoir et al.	7,572,780 B2	8/2009	Hermsmeyer
6,692,763 B1	2/2004	Cummings et al.	7,589,082 B2	9/2009	Savoir et al.
6,737,081 B2	5/2004	Savoir et al.	7,671,027 B2	3/2010	Loumaye
6,740,333 B2	5/2004	Beckett et al.	7,674,783 B2	3/2010	Hermsmeyer
6,743,815 B2	6/2004	Navaratnam et al.	7,687,281 B2	3/2010	Roth et al.
6,747,018 B2	6/2004	Tanabe et al.	7,687,485 B2	3/2010	Levinson et al.
6,756,208 B2	6/2004	Griffin et al.	7,694,683 B2	4/2010	Callister et al.
6,776,164 B2	8/2004	Bunt et al.	7,704,983 B1	4/2010	Hodgen et al.
6,787,152 B2	9/2004	Kirby et al.	7,727,720 B2	6/2010	Dhallan
6,805,877 B2	10/2004	Massara et al.	7,732,408 B2	6/2010	Josephson et al.
6,809,085 B1	10/2004	Elson et al.	7,749,989 B2	7/2010	Hill et al.
6,818,226 B2	11/2004	Reed et al.	7,862,552 B2	1/2011	McIntyre et al.
6,841,716 B1	1/2005	Tsutsumi	7,867,990 B2	1/2011	Schultz et al.
6,844,334 B2	1/2005	Hill et al.	7,879,830 B2	2/2011	Wiley
6,855,703 B1	2/2005	Hill et al.	7,884,093 B2	2/2011	Creasy et al.
6,860,859 B2	3/2005	Mehrotra et al.	7,939,104 B2	5/2011	Barbera et al.
6,866,865 B2	3/2005	Hsia et al.	7,943,602 B2	5/2011	Bunschoten et al.
6,869,969 B2	3/2005	Hubner et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
6,878,518 B2	4/2005	Whitehead	7,989,436 B2	8/2011	Hill et al.
6,901,278 B1	5/2005	Notelovitz	7,989,487 B2	8/2011	Welsh et al.
6,905,705 B2	6/2005	Palm et al.	8,022,053 B2	9/2011	Mueller et al.
6,911,438 B2	6/2005	Wright	8,048,869 B2	11/2011	Bunschoten et al.
6,923,988 B2	8/2005	Patel et al.	8,071,729 B2	12/2011	Giles-Komar et al.
6,924,274 B2	8/2005	Lardy et al.	8,076,319 B2	12/2011	Leonard
6,932,983 B1	8/2005	Straub et al.	8,088,605 B2	1/2012	Beaudet et al.
6,939,558 B2	9/2005	Massara et al.	8,101,209 B2	1/2012	Legrand et al.
6,943,021 B2	9/2005	Klausner et al.	8,101,773 B2	1/2012	Smith
6,958,327 B1	10/2005	Hillisch et al.	8,114,434 B2	2/2012	Sasaki et al.
6,962,691 B1	11/2005	Lulla et al.	8,158,614 B2	4/2012	Lambert et al.
6,962,908 B2	11/2005	Aloba et al.	8,182,833 B2	5/2012	Hermsmeyer
6,967,194 B1	11/2005	Matsuo et al.	8,202,736 B2	6/2012	Mous et al.
6,977,250 B2	12/2005	Rodriguez	8,217,024 B2	7/2012	Ahmed et al.
6,978,945 B2	12/2005	Wong et al.	8,222,008 B2	7/2012	Thoene
7,005,429 B2	2/2006	Dey et al.	8,227,454 B2	7/2012	Hill et al.
7,011,846 B2	3/2006	Shojaei et al.	8,227,509 B2	7/2012	Castro et al.
7,018,992 B2	3/2006	Koch et al.	8,241,664 B2	8/2012	Dudley et al.
7,030,157 B2	4/2006	Ke et al.	8,247,393 B2	8/2012	Ahmed et al.
RE39,104 E	5/2006	Duclos et al.	8,273,730 B2	9/2012	Fernandez et al.
7,074,779 B2	7/2006	Sue et al.	8,287,888 B2	10/2012	Song et al.
7,083,590 B1	8/2006	Bunt et al.	8,329,680 B2	12/2012	Evans et al.
7,091,213 B2	8/2006	Metcalf, III et al.	8,349,820 B2	1/2013	Zeun et al.
7,101,342 B1	9/2006	Caillouette	8,420,111 B2	4/2013	Hermsmeyer
7,135,190 B2	11/2006	Piao et al.	8,435,561 B2	5/2013	Besins et al.
7,163,681 B2	1/2007	Giles-Komar et al.	8,658,628 B2	2/2014	Baucom
7,163,699 B2	1/2007	Besse	8,663,681 B2	3/2014	Ahmed et al.
7,179,799 B2	2/2007	Hill et al.	2001/005728 A1	6/2001	Guittard et al.
7,196,074 B2	3/2007	Blye et al.	2001/0021816 A1	9/2001	Caillouette
7,198,801 B2	4/2007	Carrara et al.	2001/0027189 A1	10/2001	Bennink et al.
7,226,910 B2	6/2007	Wilson et al.	2001/0029357 A1	10/2001	Bunt et al.
7,247,625 B2	7/2007	Zhang et al.	2001/0031747 A1	10/2001	DeZiegler et al.
7,250,446 B2	7/2007	Sangita et al.	2001/0034340 A1	10/2001	Pickar
7,267,829 B2	9/2007	Kirby et al.	2001/0056068 A1	12/2001	Chwalisz et al.
7,300,926 B2	11/2007	Prokai et al.	2002/0012710 A1	1/2002	Lansky
7,303,763 B2	12/2007	Ho	2002/0026158 A1	2/2002	Rathbone et al.
7,317,037 B2	1/2008	Fensome et al.	2002/0028788 A1	3/2002	Bunt et al.
7,329,654 B2	2/2008	Kanojia et al.	2002/0058648 A1	5/2002	Hammerly
7,335,650 B2	2/2008	Potter et al.	2002/0058926 A1	5/2002	Rathbone et al.
7,374,779 B2	5/2008	Chen et al.	2002/0076441 A1	6/2002	Shih et al.
7,378,404 B2	5/2008	Peters			
7,387,789 B2	6/2008	Klose et al.			

US 8,846,648 B2

Page 4

(56)

References Cited**U.S. PATENT DOCUMENTS**

2002/0102308 A1	8/2002	Wei et al.	2005/0025833 A1	2/2005	Aschkenasy et al.
2002/0107230 A1	8/2002	Waldon et al.	2005/0031651 A1	2/2005	Gervais et al.
2002/0114803 A1	8/2002	Deaver et al.	2005/0042173 A1	2/2005	Besse et al.
2002/0132801 A1	9/2002	Heil et al.	2005/0042268 A1	2/2005	Aschkenasy et al.
2002/0137749 A1	9/2002	Levinson et al.	2005/0048116 A1	3/2005	Straub et al.
2002/0151530 A1	10/2002	Leonard et al.	2005/0079138 A1	4/2005	Chickering, III et al.
2002/0156394 A1	10/2002	Mehrotra et al.	2005/0085453 A1	4/2005	Govindarajan
2002/0169150 A1	11/2002	Pickar	2005/0101579 A1	5/2005	Shippen
2002/0173510 A1	11/2002	Levinson et al.	2005/0113350 A1	5/2005	Duesterberg et al.
2002/0193356 A1	12/2002	Van Beek et al.	2005/0118272 A1	6/2005	Besse et al.
2003/0004145 A1	1/2003	Leonard	2005/0153946 A1	7/2005	Hirsh et al.
2003/0007994 A1	1/2003	Bunt et al.	2005/0164977 A1	7/2005	Coelingh Bennink
2003/0049307 A1	3/2003	Gyurik	2005/0182105 A1	8/2005	Nirschl et al.
2003/0064097 A1	4/2003	Patel et al.	2005/0187267 A1	8/2005	Hamann et al.
2003/0072760 A1	4/2003	Sirbasku	2005/0192253 A1	9/2005	Salvati et al.
2003/0073248 A1	4/2003	Roth et al.	2005/0192310 A1	9/2005	Gavai et al.
2003/0073673 A1	4/2003	Hesch	2005/0207990 A1	9/2005	Funke et al.
2003/0077297 A1	4/2003	Chen et al.	2005/0214384 A1	9/2005	Juturu et al.
2003/0078245 A1	4/2003	Bennink et al.	2005/0220825 A1	10/2005	Funke et al.
2003/0091640 A1	5/2003	Ramanathan et al.	2005/0222106 A1	10/2005	Bracht
2003/0092691 A1	5/2003	Besse et al.	2005/0244522 A1	11/2005	Carrara et al.
2003/0096012 A1	5/2003	Besse et al.	2005/0245902 A1	11/2005	Cornish et al.
2003/0104048 A1	6/2003	Patel et al.	2005/0250746 A1	11/2005	Iammatteo
2003/0114420 A1	6/2003	Salvati et al.	2005/0250750 A1	11/2005	Cummings et al.
2003/0114430 A1	6/2003	MacLeod et al.	2005/0250753 A1	11/2005	Fink et al.
2003/0124182 A1	7/2003	Shojaei et al.	2005/0256028 A1	11/2005	Yun et al.
2003/0124191 A1	7/2003	Besse et al.	2005/0266078 A1	12/2005	Jorda et al.
2003/0130558 A1	7/2003	Massara et al.	2005/0271598 A1	12/2005	Friedman et al.
2003/0144258 A1	7/2003	Heil et al.	2005/0272712 A1	12/2005	Grubb et al.
2003/0157157 A1	8/2003	Luo et al.	2006/0014728 A1	1/2006	Chwalisz et al.
2003/0166509 A1	9/2003	Edwards et al.	2006/0018937 A1	1/2006	Friedman et al.
2003/0180352 A1	9/2003	Patel et al.	2006/0019978 A1	1/2006	Balog
2003/0181353 A1	9/2003	Nyce	2006/0020002 A1	1/2006	Salvati et al.
2003/0181728 A1	9/2003	Salvati et al.	2006/0030615 A1	2/2006	Fensome et al.
2003/0191096 A1	10/2003	Leonard et al.	2006/0034889 A1	2/2006	Jo et al.
2003/0195177 A1	10/2003	Leonard et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2003/0215496 A1	11/2003	Patel et al.	2006/0052341 A1	3/2006	Cornish et al.
2003/0220297 A1	11/2003	Berstein et al.	2006/0069031 A1	3/2006	Loumaye
2003/0224057 A1	12/2003	Martin-Letellier et al.	2006/0083778 A1	4/2006	Allison et al.
2003/0224059 A1	12/2003	Lerner et al.	2006/0089337 A1	4/2006	Casper et al.
2003/0225050 A1	12/2003	Grawe et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2003/0228686 A1	12/2003	Klausner et al.	2006/0106004 A1	5/2006	Brody et al.
2003/0229057 A1	12/2003	Caubel et al.	2006/0110415 A1	5/2006	Gupta
2004/0009960 A1	1/2004	Heil et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0034001 A1	2/2004	Karara	2006/0121626 A1	6/2006	Imrich
2004/0037881 A1	2/2004	Guittard et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2004/0043943 A1	3/2004	Guittard et al.	2006/0135619 A1	6/2006	Kick et al.
2004/0044080 A1	3/2004	Place et al.	2006/0194775 A1	8/2006	Tofovic et al.
2004/0052824 A1	3/2004	Chacra-Vernet et al.	2006/0204557 A1	9/2006	Gupta et al.
2004/0073024 A1	4/2004	Metcalf, III et al.	2006/0235037 A1	10/2006	Purandare et al.
2004/0077605 A1	4/2004	Salvati et al.	2006/0240111 A1	10/2006	Fernandez et al.
2004/0077606 A1	4/2004	Salvati et al.	2006/0247216 A1	11/2006	Haj-Yehia
2004/0087548 A1	5/2004	Salvati et al.	2006/0252049 A1	11/2006	Shuler et al.
2004/0089308 A1	5/2004	Welch	2006/0257472 A1	11/2006	Nielsen
2004/0092583 A1	5/2004	Shahanan-Prendergast	2006/0275360 A1	12/2006	Ahmed et al.
2004/0097468 A1	5/2004	Wimalawansa	2006/0280771 A1	12/2006	Groenewegen et al.
2004/0101557 A1	5/2004	Gibson et al.	2006/0280797 A1	12/2006	Shoichet et al.
2004/0106542 A1	6/2004	Deaver et al.	2006/0280800 A1	12/2006	Nagi et al.
2004/0131670 A1	7/2004	Gao	2007/0004693 A1	1/2007	Woolfson et al.
2004/0142012 A1	7/2004	Bunt et al.	2007/0004694 A1	1/2007	Woolfson et al.
2004/0146894 A1	7/2004	Warrington et al.	2007/0021360 A1	1/2007	Nyce et al.
2004/0176324 A1	9/2004	Salvati et al.	2007/0027201 A1	2/2007	McComas et al.
2004/0176336 A1	9/2004	Rodriguez	2007/0031491 A1	2/2007	Levine et al.
2004/0185104 A1	9/2004	Piao et al.	2007/0042038 A1	2/2007	Besse
2004/0191276 A1	9/2004	Muni	2007/0060589 A1	3/2007	Purandare et al.
2004/0198706 A1	10/2004	Carrara	2007/0066628 A1	3/2007	Zhang et al.
2004/0213744 A1	10/2004	Lulla et al.	2007/0066637 A1	3/2007	Zhang et al.
2004/0234606 A1	11/2004	Levine et al.	2007/0066675 A1	3/2007	Zhang et al.
2004/0253319 A1	12/2004	Netke et al.	2007/0088029 A1	4/2007	Balog et al.
2004/0259817 A1	12/2004	Waldon et al.	2007/0093548 A1	4/2007	Diffendal et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2007/0116729 A1	5/2007	Palepu
2005/0004088 A1	1/2005	Hesch	2007/0116829 A1	5/2007	Prakash et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2007/0178166 A1	8/2007	Bernstein et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2007/0184558 A1	8/2007	Roth et al.
2005/0021009 A1	1/2005	Massara et al.	2007/0191319 A1	8/2007	Ke et al.
			2007/0196433 A1	8/2007	Ron et al.
			2007/0207225 A1	9/2007	Squadrito
			2007/0225281 A1	9/2007	Zhang et al.
			2007/0238713 A1	10/2007	Gast et al.

US 8,846,648 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2007/0243229 A1	10/2007	Smith et al.	2011/0053845 A1	3/2011	Levine et al.	
2007/0264309 A1	11/2007	Chollet et al.	2011/0076775 A1	3/2011	Stewart et al.	
2007/0264345 A1	11/2007	Eros et al.	2011/0076776 A1	3/2011	Stewart et al.	
2007/0264349 A1	11/2007	Lee et al.	2011/0086825 A1	4/2011	Chatroux	
2007/0286819 A1	12/2007	DeVries et al.	2011/0091555 A1	4/2011	De Luigi Bruschi et al.	
2007/0287789 A1	12/2007	Jones et al.	2011/0098631 A1	4/2011	Mcintyre et al.	
2007/0292387 A1	12/2007	Jon et al.	2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	
2008/0026035 A1	1/2008	Chollet et al.	2011/0135719 A1	6/2011	Besins et al.	
2008/0026062 A1	1/2008	Farr et al.	2011/0182997 A1	7/2011	Lewis et al.	
2008/0038350 A1	2/2008	Gerecke et al.	2011/0195114 A1	8/2011	Carrara et al.	
2008/0085877 A1	4/2008	Bortz	2011/0195944 A1	8/2011	Mura et al.	
2008/0095838 A1	4/2008	Abou Chacra-Vernet	2011/0217341 A1	9/2011	Sah	
2008/0113953 A1	5/2008	De Vries et al.	2011/0250274 A1	10/2011	Shaked et al.	
2008/0114050 A1	5/2008	Fensome et al.	2011/0256092 A1	10/2011	Phiasivongsa et al.	
2008/0119537 A1	5/2008	Zhang et al.	2011/0262494 A1	10/2011	Achleitner et al.	
2008/0125402 A1	5/2008	Diliberti et al.	2011/0268665 A1	11/2011	Tamarkin et al.	
2008/0138379 A1	6/2008	Jennings-Spring	2011/0293720 A1	12/2011	General et al.	
2008/0145423 A1	6/2008	Khan et al.	2011/0311592 A1	12/2011	Birbara	
2008/0175814 A1	7/2008	Phiasivongsa et al.	2011/0312927 A1	12/2011	Nachaegari et al.	
2008/0188829 A1	8/2008	Creasy	2011/0312928 A1	12/2011	Nachaegari et al.	
2008/0206161 A1	8/2008	Tamarkin et al.	2012/009276 A1	1/2012	De Groote	
2008/0220069 A1	9/2008	Allison	2012/0015350 A1	1/2012	Nabatiyan et al.	
2008/0234199 A1	9/2008	Katamreddym	2012/0045532 A1	2/2012	Cohen	
2008/0255078 A1	10/2008	Katamreddym	2012/0269878 A2	2/2012	Cantor et al.	
2008/0255089 A1	10/2008	Katamreddym	2012/0052077 A1	3/2012	Truitt et al.	
2008/0299220 A1	12/2008	Tamarkin et al.	2012/0128625 A1	5/2012	Shalwitz et al.	
2008/0306036 A1	12/2008	Katamreddym	2012/0128777 A1	5/2012	Keck et al.	
2008/0312197 A1	12/2008	Rodriguez	2012/0149748 A1	6/2012	Shanler et al.	
2008/0312198 A1	12/2008	Rodriguez	2012/0269721 A1	10/2012	Weng et al.	
2008/0319078 A1	12/2008	Katamreddym	2012/0283671 A1	11/2012	Shibata et al.	
2009/0053294 A1	2/2009	Prendergast	2013/0022674 A1	1/2013	Dudley et al.	
2009/0060982 A1	3/2009	Ron et al.	2013/0029947 A1	1/2013	Nachaegari et al.	
2009/0068118 A1	3/2009	Eini et al.	2013/0129818 A1	5/2013	Bernick et al.	
2009/0081278 A1	3/2009	De Graaff et al.	FOREIGN PATENT DOCUMENTS			
2009/0081303 A1	3/2009	Savoir et al.	EP	0785212 A1	7/1997	
2009/0092656 A1	4/2009	Klamerus et al.	EP	1094781 B1	7/2008	
2009/0099106 A1	4/2009	Phiasivongsa et al.	EP	2191833 A1	6/2010	
2009/0131385 A1	5/2009	Voskuhl	GB	1589946 A1	2/1921	
2009/0137478 A1	5/2009	Bernstein et al.	GB	452238 A	8/1936	
2009/0137538 A1	5/2009	Klamerus et al.	GB	720561 A	12/1954	
2009/0143344 A1	6/2009	Chang	GB	848881 A	9/1960	
2009/0181088 A1	7/2009	Song et al.	GB	874368 A	8/1961	
2009/0214474 A1	8/2009	Jennings	IN	216026 A	3/2008	
2009/0227025 A1	9/2009	Nichols et al.	IN	2005KO00053 A	9/2009	
2009/0232897 A1	9/2009	Sahoo et al.	IN	244217 A	11/2010	
2009/0258096 A1	10/2009	Cohen	WO	9011064 A1	10/1990	
2009/0264395 A1	10/2009	Creasy	WO	9317686 A1	9/1993	
2009/0269403 A1	10/2009	Shaked et al.	WO	9422426 A1	10/1994	
2009/0285772 A1	11/2009	Phiasivongsa et al.	WO	9530409 A1	11/1995	
2009/0318558 A1	12/2009	Kim et al.	WO	9609826 A2	4/1996	
2009/0325916 A1	12/2009	Zhang et al.	WO	9630000 A1	10/1996	
2010/0028360 A1	2/2010	Atwood	WO	9705491	2/1997	
2010/0040671 A1	2/2010	Ahmed et al.	WO	9743989 A1	11/1997	
2010/0048523 A1	2/2010	Bachman et al.	WO	9810293 A1	3/1998	
2010/0303825 A9	2/2010	Sirkasku	WO	9832465 A1	7/1998	
2010/0074959 A1	3/2010	Hansom et al.	WO	9851280 A1	11/1998	
2010/0086599 A1	4/2010	Huempel et al.	WO	9932072 A1	7/1999	
2010/0092568 A1	4/2010	Lerner et al.	WO	9939700 A1	8/1999	
2010/0105071 A1	4/2010	Laufer et al.	WO	9942109 A1	8/1999	
2010/0129320 A1	5/2010	Phiasivongsa et al.	WO	9943304 A1	9/1999	
2010/0136105 A1	6/2010	Chen et al.	WO	9948477 A1	9/1999	
2010/0137265 A1	6/2010	Leonard	WO	9953910 A2	10/1999	
2010/0137271 A1	6/2010	Chen et al.	WO	0038659 A1	11/1999	
2010/0152144 A1	6/2010	Hermsmeyer	WO	9963974 A2	12/1999	
2010/0168228 A1	7/2010	Bose et al.	WO	0001351 A1	1/2000	
2010/0183723 A1	7/2010	Laurent-Applegate	WO	0006175 A1	2/2000	
2010/0184736 A1	7/2010	Coelingh Bennink et al.	WO	0045795 A2	8/2000	
2010/0190758 A1	7/2010	Fauser et al.	WO	0050007 A1	8/2000	
2010/0240626 A1	9/2010	Kulkarni et al.	WO	0059577 A1	10/2000	
2010/0247632 A1	9/2010	Dong et al.	WO	0137808 A1	11/2000	
2010/0255085 A1	10/2010	Liu et al.	WO	0076522 A1	12/2000	
2010/0312137 A1	12/2010	Gilmour et al.	WO	0154699 A1	8/2001	
2010/0316724 A1	12/2010	Whitfield et al.	WO	0160325 A1	8/2001	
2010/0330168 A1	12/2010	Gicquel et al.	WO	0207700 A2	2/2002	
2011/0028439 A1	2/2011	Witt-Enderby et al.	WO	0211768 A1	2/2002	
			WO	0222132 A2	3/2002	
			WO	0240008 A2	5/2002	

US 8,846,648 B2

Page 6

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO 02053131 A1 7/2002
 WO 02078602 A2 10/2002
 WO 2002078604 A2 10/2002
 WO 03041718 A1 5/2003
 WO 03041741 A1 5/2003
 WO 03068186 A1 8/2003
 WO 03077923 A1 9/2003
 WO 03082254 A1 10/2003
 WO 03092588 A2 11/2003
 WO 2004017983 A1 3/2004
 WO 2005027911 A1 3/2004
 WO 2004032897 A2 4/2004
 WO 2004052336 A2 6/2004
 WO 2004054540 A2 7/2004
 WO 2004080413 A2 9/2004
 WO 2005030175 A1 4/2005
 WO 2005087194 A1 9/2005
 WO 2005087199 A2 9/2005
 WO 2005105059 A1 11/2005
 WO 2005115335 A1 12/2005
 WO 2005120470 A1 12/2005
 WO 2005120517 A1 12/2005
 WO 2006013369 A2 2/2006
 WO 2006034090 A1 3/2006
 WO 2006036899 A2 4/2006
 WO 2006053172 A2 5/2006
 WO 2006105615 A1 10/2006
 WO 2006113505 A2 10/2006
 WO 2006138686 A1 12/2006
 WO 2006138735 A2 12/2006
 WO 2007045027 A1 4/2007
 WO 2007103294 A2 9/2007
 WO 2007123790 A1 11/2007
 WO 2007124250 A2 11/2007
 WO 2007144151 A1 12/2007
 WO 2008049516 A3 5/2008
 WO 2008152444 A2 12/2008
 WO 2009002542 A1 12/2008
 WO 2009036311 A1 3/2009
 WO 2009040818 A4 4/2009
 WO 2009069006 A2 6/2009
 WO 2009098072 A2 8/2009
 WO 2009133352 A2 11/2009
 WO 2010033188 A2 3/2010
 WO 2011000210 A1 1/2011
 WO 2011073995 A2 6/2011
 WO 2011120084 A1 10/2011
 WO 2011128336 A1 10/2011
 WO 2012009778 A2 1/2012
 WO 2012024361 A1 2/2012
 WO 2013192248 A1 12/2013
 WO 2013192249 A1 12/2013
 WO 2013192250 A1 12/2013
 WO 2013192251 A1 12/2013

OTHER PUBLICATIONS

International Search Report and Written Opinion for related International Application No. PCT/US12/066406 dated Jan. 24, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/046442 dated Nov. 1, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/046443 dated Oct. 31, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/046444 dated Oct. 31, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/046445 dated Nov. 1, 2013.
 USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.
 USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.

USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.
 Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.
 Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.
 Azure Pharma, Inc., "ELESTRIINTM—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages (Aug. 2009).
 Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER_A and ER_B," Endocrinology, 149(10): 4857-4870 (Oct. 2008).
 Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).
 Tahition Noni, "Body Balance Cream," http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/, (undated), 1 page.
 Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.
 Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).
 Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).
 Diramio, "Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia-Masters of Science Thesis, 131 pages (2004). http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1.
 Du, et al. "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," Menopause: The Journal of The North American Menopause Society, vol. 20, No. 11, (Feb. 2013).
 Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.
 Fuchs, et al., "The Effects of on Estrogen and Glycolic Acid Cream on the Focal Skin of Postmenopausal Women: A Randomized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.
 Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.
 Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.
 Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).
 Kincl, et al., "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.
 Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.
 Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Periestrual and Postinsemination Periods in Dairy Cattle," Biol Reprod. 35(2):300-311 (1986). Abstract Only.
 Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.
 NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.

US 8,846,648 B2

Page 7

(56)

References Cited**OTHER PUBLICATIONS**

- Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, min.sagepub.com. Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
- Panchagnula et al., "Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," J Pharm Pharmacol. 43(9):609-614 (Sep. 1991). Abstract Only.
- Patel, et al., "Transdermal Drug Delivery System: A Review," www.thepharmajournal.com, vol. 1 No. 4 2012.
- Salole, "The physiochemical properties of oestradiol," Journal of Pharmaceutical & Biomedical Analysis, 5 (7):635-648 (1987).
- Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," American Journal of Public Health, Published online ahead of print Jul. 18, 2013.
- Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014.
- Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," The American College of Obstetricians and Gynecologists, vol. 112, No. 5, Nov. 2008.
- Sitruk-Ware, et al., "Oral Micronized Progesterone," Department of Reproductive Endocrinology, vol. 36, No. 4, pp. 373-402, Oct. 1987.
- Sitruk-Ware, et al., "Progesterogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," Menopause: The Journal of the North American Menopause Society, vol. 9, No. 1, pp. 6-15, 2002.
- Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," JAMA Internal Medicine http://archinte.jamanetwork.com, Sep. 30, 2013.
- Stanczyk, et al. "Ethynodiol and 17 β -Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment" Departments of Obstetrics and Gynecology and Preventive Medicine, University of Southern California Keck School of Medicine, Contraception 87 706-727, (2013).
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," Pharmaceutical Research, 21(2):201-230 (Feb. 2004).
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," Skin Pharmacol Physiol, 19:106-121 (2006). http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf.
- Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," The British Medical Journal, vol. 280, No. 6217, Mar. 22, 1980.
- Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," Springer Science+Business Media B.V., Breast Cancer Res Treat 101:125-134, (2007).
- USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II. vol. 1 pp. 127-139, 1968, Mikrochimica Acta.
- Kuhnert-Brandstaetter, M & Lnder, R, Zur Hydratbildung bei Steroidhormonen, Sci. Pharm., vol. 41(2) pp. 109-116, 1973.
- Kuhnert-Brandstaetter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, Microchemical Journal 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, Journal of Steroid Biochemistry & Molecular Biology, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr, The WHI ten year's later: An epidemiologist's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , Jour. of Pharm. Sci., vol. 96(12) pp. 3419-31, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, Pharmaceutical Research, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, Fertility and Sterility, vol. 79(1), Jan. 2003.
- Lewis, John G, et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , Maturitas, The European Menopaus Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , Steroids, Elsevier, vol. 77, pp. 185-92, 2012.
- Lobo, R.A., Foreword, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, J Thermal Anal., vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , Journal of Animal Science, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, Chemistry and Industry, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, J. Steroid Biochem. Mol.Biol. (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, J. Pharmaceutical Sciences, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , Drug Devel. & Indust. Pharmacy, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , Clinical Endocrinology, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, Arch Pharm Res, vol. 31(1), pp. 111-116, 2008.

US 8,846,648 B2

Page 8

(56)

References Cited

OTHER PUBLICATIONS

- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , European Journal of Pharmaceutics and Biopharmaceutics, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, Crystal Structure Comm., Int'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, Intl. Jour. of Pharma., vol. 177 pp. 231-45, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Pisegna, Gisia L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, Adv. Drug Delivery Reviews, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, Pharmaceutical Research, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , J Steroids Horm Sci, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, Asian J. Chem., vol. 9 (3) pp. 418-26, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Forest!, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H. C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>, (2014).
- ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, Obstetrics & Gynecology.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette (2014).
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>, (2014).
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moleculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helveticae, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

US 8,846,648 B2

Page 9

(56)

References Cited

OTHER PUBLICATIONS

- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-6671, 2000, Elsevier.
- Krzyminewski, R, et al., EPR Study of the Stable Radical in a γ -radiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Abitec, CapmuIMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmuIMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmuIMCM, Safety Data Sheet, 2011, Janesville, WI.
- Abitec, CapmuIMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmuIPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of *Thevetia peruviana* and *Hura crepitans* Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, *Ph. Eur. Monograph 1342*, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, *Chempro-Edible-Oil-Refining-ISO-TUV-Austria*, (2014).
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A, et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Brazil.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant Water, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Suplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.

US 8,846,648 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helveticae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.

- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. SteroidBiochem. Mol. Biol.* (2013), Elsevier.
- Wiranichapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yue, W, Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.
- US 6,214,374, 04/2001, Schmirler et al. (withdrawn)

* cited by examiner

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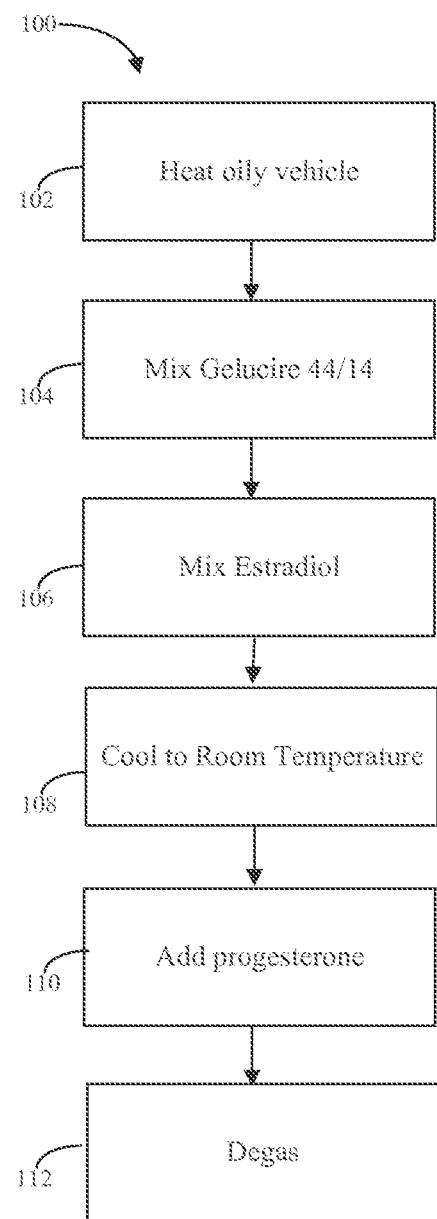
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Fig. 1

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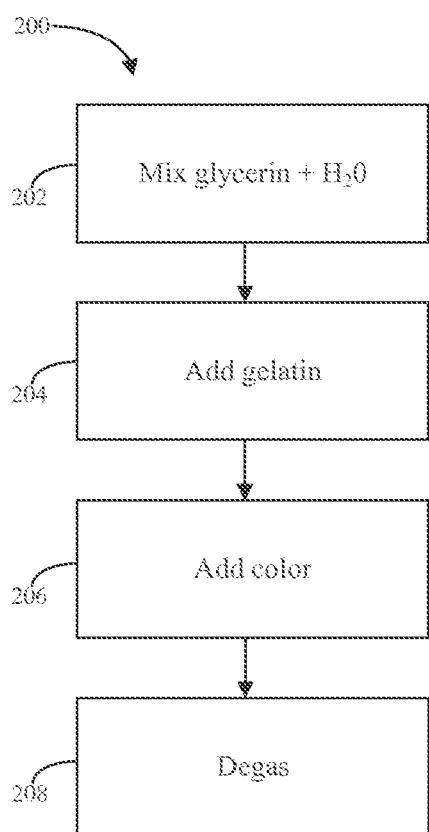


Fig. 2

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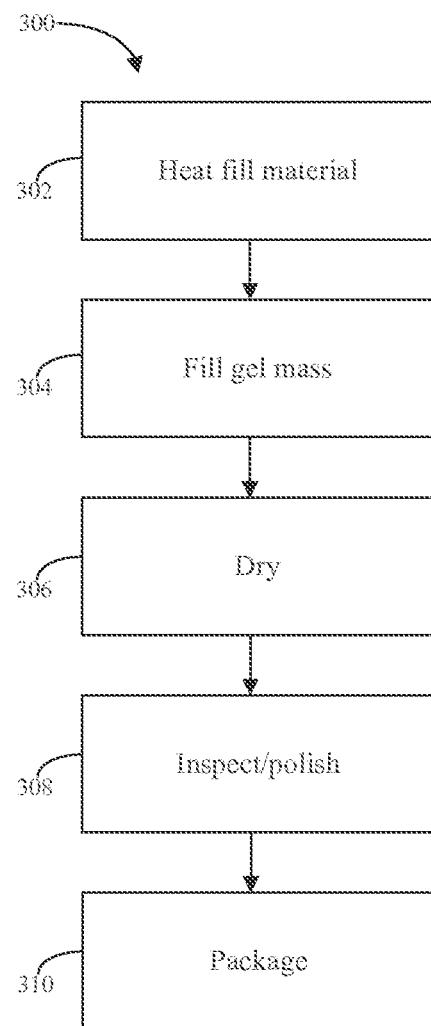


Fig. 3

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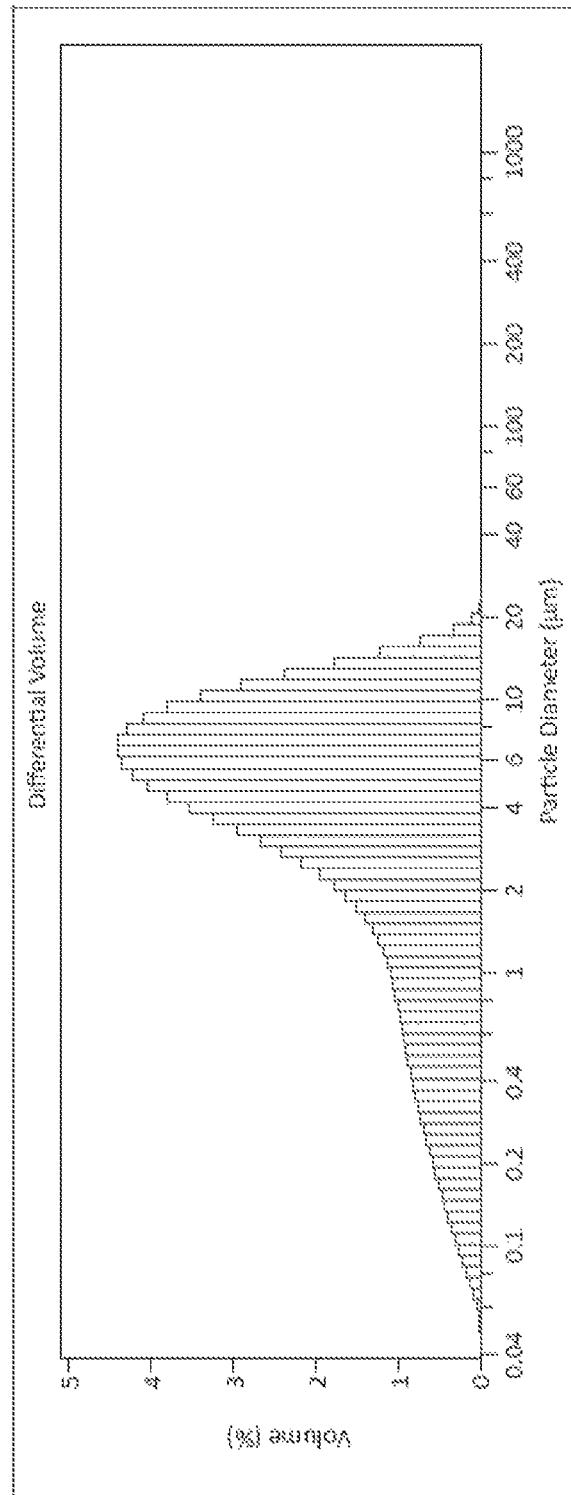


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a non-provisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563, 408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREMPRO (conjugated estrogens/methoxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus methoxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic methoxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

**BRIEF DESCRIPTION OF THE
DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

**DETAILED DESCRIPTION OF THE
ILLUSTRATED EMBODIMENTS**

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max}, and optionally, T_{max}.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, "C_{max}" as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, "T_{max}" as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

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The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

10 "Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

15 Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

30 35 Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

60 Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal

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dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans; for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary

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dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil;

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generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be

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solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

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As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth hereinabove, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate,

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medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40

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TABLE 2-continued

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride): CAPMUL (a propylene glycol monocaprylate; propylene glycol monicaprate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monoca-

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prylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	322.97	99.38	3.23 kg
Total	100	3.25 kg	

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The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-

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32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides) GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF	82.57	577.97	
TOTAL	100.00		700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and

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CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

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TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

40 In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w (mg)	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

65 For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2%

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w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

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Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF		10.0	70.00	0.70
	Total:	100.00	700.00	7.00	

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
	Total:	100.000	200.00 mg	2000.00	

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C.

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GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	Qty/ % w/w Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32	391.93
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0
Total:		100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

Progesterone and Estradiol Combination Study under Fed Conditions.

This following study protocol was used to establish bioavailability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

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Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration

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of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled

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volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A method of treating a menopause-related symptom in a woman comprising:
administering to the woman an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent;
wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;
wherein the solubilizing agent contains an effective amount of C6-C12 oil; and
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent.
2. The method of claim 1, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.
3. The method of claim 1, wherein the composition is formulated as a gelatin capsule.
4. The method of claim 1, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.
5. The method of claim 1, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

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6. The method of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

7. The method of claim 1, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and to a 2 mg estradiol tablet.

8. A method of treating a menopause symptom in a woman comprising administering a pharmaceutical composition to the woman, the pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent, the solubilizing agent containing an effective amount of a C6-C12 oil;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

9. The method of claim 8, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

10. The method of claim 8, wherein the composition is formulated as a gelatin capsule.

11. The method of claim 8, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

12. The method of claim 8, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

13. The method of claim 8, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

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14. The method of claim 8, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and to a 2 mg estradiol tablet.

15. A method of treating a menopause symptom comprising:

administering an effective amount of a pharmaceutical composition to a woman, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent, the estradiol being stable in the solubilizing agent for at least 14 days; wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent, and wherein the solubilizing agent contains an effective amount of a C6-C12 oil.

16. The method of claim 15, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

17. The method of claim 15, wherein the composition is formulated as a gelatin capsule.

18. The method of claim 15, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

19. The method of claim 15, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

20. The method of claim 15, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,846,648 B2
APPLICATION NO. : 14/099545
DATED : September 30, 2014
INVENTOR(S) : Brian A. Bernick et al.

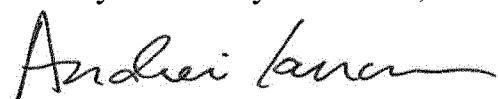
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,846,648 B2
APPLICATION NO. : 14/099545
DATED : September 30, 2014
INVENTOR(S) : Brian A. Bernick et al.

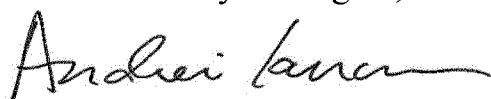
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 24, Claim 15, Line 16: Delete “agnent” and insert in its place --agent--.

Signed and Sealed this
Twentieth Day of August, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT C



US008846649B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,846,649 B2**
(45) **Date of Patent:** ***Sep. 30, 2014**

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/099,571**

(22) Filed: **Dec. 6, 2013**

(65) **Prior Publication Data**

US 2014/0094440 A1 Apr. 3, 2014

3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Higuchi et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes
4,012,496 A	3/1977	Hartmann
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	van Der Vies
4,093,709 A	6/1978	Choi
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong
4,237,885 A	12/1980	Wong
4,310,510 A	1/1982	Sherman et al.
4,327,725 A	5/1982	Cortese et al.
4,372,951 A	2/1983	Vorys
4,384,096 A	5/1983	Sonnabend
4,393,871 A	7/1983	Vorhauer
4,402,695 A	9/1983	Wong
4,423,151 A	12/1983	Baranczuk
4,449,980 A	5/1984	Millar et al.
4,610,687 A	9/1986	Fogwell
4,629,449 A	12/1986	Wong

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI 1001367-9 A2	7/2012
CN	102258455 A	11/2011

(Continued)

OTHER PUBLICATIONS

US 6,214,374, 4/2001, Schmirler, et al. (withdrawn).
International Search Report and Written Opinion for related International Application No. PCT/US12/066406 dated Jan. 24, 2013.
International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.

(Continued)

Primary Examiner — Frederick Krass

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(51) **Int. Cl.**

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<i>A61K 9/16</i>	(2006.01)
<i>A61K 31/57</i>	(2006.01)
<i>A61K 31/565</i>	(2006.01)

(52) **U.S. Cl.**

CPC	<i>A61K 31/57</i> (2013.01); <i>A61K 9/4858</i> (2013.01); <i>A61K 9/16</i> (2013.01); <i>A61K 31/565</i> (2013.01)
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USPC **514/169**; 424/452

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934	Doisy
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Grant et al.
3,198,707 A	8/1965	Nomaine et al.
3,478,070 A	11/1969	Smith et al.
3,526,648 A	9/1970	Bertin et al.

ABSTRACT

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

15 Claims, 4 Drawing Sheets

US 8,846,649 B2

Page 2

(56)

References Cited**U.S. PATENT DOCUMENTS**

4,732,763 A	3/1988	Beck et al.	5,922,349 A	7/1999	Elliesen et al.
4,738,957 A	4/1988	Laurent et al.	5,928,666 A	7/1999	Farinas et al.
4,756,907 A	7/1988	Beck et al.	5,958,446 A	9/1999	Miranda et al.
4,762,717 A	8/1988	Crowley	5,962,445 A	10/1999	Stewart
4,788,062 A	11/1988	Gale et al.	5,972,372 A	10/1999	Saleh et al.
4,816,257 A	3/1989	Buster et al.	5,985,861 A	11/1999	Levine et al.
4,822,616 A	4/1989	Zimmermann et al.	5,993,856 A	11/1999	Ragavan et al.
4,865,848 A	9/1989	Cheng et al.	6,001,846 A	12/1999	Edwards et al.
4,900,734 A	2/1990	Maxson et al.	6,022,562 A	2/2000	Autant et al.
4,906,475 A	3/1990	Kim	6,024,976 A	2/2000	Miranda et al.
4,942,158 A	7/1990	Sarpotdar et al.	6,028,057 A	2/2000	Burns
4,961,931 A	10/1990	Wong	6,039,968 A	3/2000	Nabahi
5,030,629 A	7/1991	Rajadhyaksha	6,056,972 A	5/2000	Hermsmeyer
5,064,654 A	11/1991	Berner et al.	6,060,077 A	5/2000	Meignant
5,108,995 A	4/1992	Casper	6,074,625 A	6/2000	Hawthorne et al.
5,128,138 A	7/1992	Blank	6,077,531 A	6/2000	Salin-Drouin
5,130,137 A	7/1992	Crowley	6,080,118 A	6/2000	Blythe
5,140,021 A	8/1992	Maxson et al.	6,083,178 A	7/2000	Caillouette
5,211,952 A	5/1993	Pike et al.	6,086,916 A	7/2000	Agnus et al.
5,252,334 A	10/1993	Chiang et al.	6,096,338 A	8/2000	Lacy et al.
5,280,023 A	1/1994	Ehrlich et al.	6,117,446 A	9/2000	Place
5,288,496 A	2/1994	Lewis	6,117,450 A	9/2000	Dittgen et al.
5,340,584 A	8/1994	Spicer et al.	6,133,251 A	10/2000	Dittgen et al.
5,340,585 A	8/1994	Pike et al.	6,133,320 A	10/2000	Yallampalli et al.
5,340,586 A	8/1994	Pike et al.	6,139,873 A	10/2000	Hughes, Jr. et al.
5,362,497 A	11/1994	Yamada et al.	6,153,216 A	11/2000	Cordes et al.
5,382,573 A	1/1995	Casper	6,165,491 A	12/2000	Grasset et al.
5,393,528 A	2/1995	Staab	6,165,975 A	12/2000	Adams et al.
5,393,529 A	2/1995	Hoffmann et al.	6,187,339 B1	2/2001	de Haan et al.
5,419,910 A	5/1995	Lewis	6,190,331 B1	2/2001	Caillouette
5,468,736 A	11/1995	Hodgen	6,201,072 B1	3/2001	Rathi et al.
5,474,783 A	12/1995	Miranda et al.	6,227,202 B1	5/2001	Matapurkar
5,480,776 A	1/1996	Dullien	6,262,115 B1	7/2001	Guittard et al.
5,514,673 A	5/1996	Heckenmuller et al.	6,277,418 B1	8/2001	Markaverich et al.
5,516,528 A	5/1996	Hughes et al.	6,283,927 B1	9/2001	Caillouette
5,527,534 A	6/1996	Myhling	6,287,588 B1	9/2001	Shih et al.
5,529,782 A	6/1996	Staab	6,287,693 B1	9/2001	Savoir et al.
5,543,150 A	8/1996	Bologna et al.	6,294,188 B1	9/2001	Ragavan et al.
5,547,948 A	8/1996	Barcomb	6,294,192 B1	9/2001	Patel et al.
5,565,199 A	10/1996	Page et al.	6,294,550 B1	9/2001	Place et al.
5,567,831 A	10/1996	Li	6,299,900 B1	10/2001	Reed et al.
5,569,652 A	10/1996	Beier et al.	6,306,841 B1	10/2001	Place et al.
5,582,592 A	12/1996	Kendrick	6,306,914 B1	10/2001	de Ziegler et al.
5,585,370 A	12/1996	Casper	6,309,669 B1	10/2001	Setterstrom et al.
5,595,759 A	1/1997	Wright et al.	6,309,848 B1	10/2001	Howett et al.
5,595,970 A	1/1997	Garfield et al.	6,342,491 B1	1/2002	Dey et al.
5,620,705 A	4/1997	Dong et al.	6,372,209 B1	4/2002	Chrisope
5,629,021 A	5/1997	Wright	6,372,246 B1	4/2002	Wei
5,633,011 A	5/1997	Dong et al.	6,387,390 B1	5/2002	Deaver et al.
5,633,242 A	5/1997	Ottel et al.	6,402,705 B1	6/2002	Caillouette
5,639,743 A	6/1997	Kaswan et al.	6,416,778 B1	7/2002	Ragavan et al.
5,656,286 A	8/1997	Miranda et al.	6,423,039 B1	7/2002	Rathbone et al.
5,676,968 A	10/1997	Lipp et al.	6,423,683 B1	7/2002	Heaton et al.
5,677,292 A	10/1997	Li et al.	6,436,633 B1	8/2002	Kreider et al.
5,694,947 A	12/1997	Lehtinen et al.	6,440,454 B1	8/2002	Santoro et al.
5,709,844 A	1/1998	Arbeit et al.	6,444,224 B1	9/2002	Rathbone et al.
5,735,801 A	4/1998	Caillouette	6,444,234 B1	9/2002	Kirby et al.
5,739,176 A	4/1998	Dunn et al.	6,451,339 B2	9/2002	Patel et al.
5,744,463 A	4/1998	Bair	6,451,779 B1	9/2002	Hesch
5,747,058 A	5/1998	Tipton et al.	6,455,246 B1	9/2002	Howell et al.
5,762,614 A	6/1998	Caillouette	6,455,517 B1	9/2002	Tanabe et al.
5,770,176 A	6/1998	Nargessi	6,468,526 B2	10/2002	Chrisope
5,770,219 A	6/1998	Chiang et al.	6,469,016 B1	10/2002	Place et al.
5,776,495 A	7/1998	Duclos et al.	6,472,434 B1	10/2002	Place et al.
5,788,980 A	8/1998	Nabahi	6,479,232 B1	11/2002	Howett et al.
5,789,442 A	8/1998	Garfield et al.	6,500,814 B1	12/2002	Hesch
5,811,416 A	9/1998	Chwalisz	6,503,896 B1	1/2003	Tanabe et al.
5,811,547 A	9/1998	Nakamichi et al.	6,511,969 B1	1/2003	Hermsmeyer
5,814,329 A	9/1998	Shah	6,526,980 B1	3/2003	Tracy et al.
5,827,200 A	10/1998	Caillouette	6,528,094 B1	3/2003	Savoir et al.
5,866,603 A	2/1999	Li et al.	6,537,580 B1	3/2003	Savoir et al.
5,891,868 A	4/1999	Cummings et al.	6,544,196 B2	4/2003	Caillouette
5,898,038 A	4/1999	Yallampalli et al.	6,544,553 B1	4/2003	Hsia et al.
5,916,176 A	6/1999	Caillouette	6,548,491 B2	4/2003	Tanabe et al.
RE36,247 E	7/1999	Plunkett et al.	6,551,611 B2	4/2003	Elliesen et al.
			6,569,463 B2	5/2003	Patel et al.
			6,583,129 B1	6/2003	Mazer et al.
			6,586,006 B2	7/2003	Roser et al.
			6,589,549 B2	7/2003	Shih et al.

US 8,846,649 B2

Page 3

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,593,317 B1	7/2003	De Ziegler et al.	7,465,587 B2	12/2008	Imrich	
6,610,670 B2	8/2003	Backensfeld et al.	7,470,433 B2	12/2008	Carrara et al.	
6,638,536 B2	10/2003	Savoir et al.	7,485,666 B2	2/2009	Villanueva et al.	
6,645,528 B1	11/2003	Straub et al.	7,497,855 B2	3/2009	Ausiello et al.	
6,653,298 B2	11/2003	Potter et al.	7,534,765 B2	5/2009	Gregg et al.	
6,656,929 B1	12/2003	Agnus et al.	7,550,142 B2	6/2009	Giles-Komar et al.	
6,660,726 B2	12/2003	Hill et al.	7,563,565 B1	7/2009	Matsuo et al.	
6,663,608 B2	12/2003	Rathbone et al.	7,572,779 B2	8/2009	Aloba et al.	
6,663,895 B2	12/2003	Savoir et al.	7,572,780 B2	8/2009	Hermsmeyer	
6,692,763 B1	2/2004	Cummings et al.	7,589,082 B2	9/2009	Savoir et al.	
6,737,081 B2	5/2004	Savoir et al.	7,671,027 B2	3/2010	Loumaye	
6,740,333 B2	5/2004	Beckett et al.	7,674,783 B2	3/2010	Hermsmeyer	
6,743,815 B2	6/2004	Huebner et al.	7,687,281 B2	3/2010	Roth et al.	
6,747,018 B2	6/2004	Tanabe et al.	7,687,485 B2	3/2010	Levinson et al.	
6,756,208 B2	6/2004	Griffin et al.	7,694,683 B2	4/2010	Callister et al.	
6,776,164 B2	8/2004	Bunt et al.	7,704,983 B1	4/2010	Hodgen et al.	
6,787,152 B2	9/2004	Kirby et al.	7,727,720 B2	6/2010	Dhallan	
6,805,877 B2	10/2004	Massara et al.	7,732,408 B2	6/2010	Josephson et al.	
6,809,085 B1	10/2004	Elson et al.	7,749,989 B2	7/2010	Hill et al.	
6,818,226 B2	11/2004	Reed et al.	7,767,656 B2	8/2010	Shoichet et al.	
6,841,716 B1	1/2005	Tsutsumi	7,815,949 B2	10/2010	Cohen	
6,844,334 B2	1/2005	Hill et al.	7,829,115 B2	11/2010	Besins et al.	
6,855,703 B1	2/2005	Hill et al.	RE42,012 E	12/2010	Deaver et al.	
6,860,859 B2	3/2005	Mehrotra et al.	7,858,607 B2	12/2010	Mamchur	
6,866,865 B2	3/2005	Hsia et al.	RE42,072 E	1/2011	Deaver et al.	
6,869,969 B2	3/2005	Huebner et al.	7,862,552 B2	1/2011	McIntyre et al.	
6,878,518 B2	4/2005	Whitehead	7,867,990 B2	1/2011	Schultz et al.	
6,901,278 B1	5/2005	Notelovitz	7,879,830 B2	2/2011	Wiley	
6,905,705 B2	6/2005	Palm et al.	7,884,093 B2	2/2011	Creasy et al.	
6,911,438 B2	6/2005	Wright	7,939,104 B2	5/2011	Barbera et al.	
6,923,988 B2	8/2005	Patel et al.	7,943,602 B2	5/2011	Bunschoten et al.	
6,924,274 B2	8/2005	Lardy et al.	7,943,604 B2	5/2011	Coelingh Bennik et al.	
6,932,983 B1	8/2005	Straub et al.	7,989,436 B2	8/2011	Hill et al.	
6,939,558 B2	9/2005	Massara et al.	7,989,487 B2	8/2011	Welsh et al.	
6,943,021 B2	9/2005	Klausner et al.	8,022,053 B2	9/2011	Mueller et al.	
6,958,327 B1	10/2005	Hillisch et al.	8,048,869 B2	11/2011	Bunschoten et al.	
6,962,691 B1	11/2005	Lulla et al.	8,071,729 B2	12/2011	Giles-Komar et al.	
6,962,908 B2	11/2005	Aloba et al.	8,076,319 B2	12/2011	Leonard	
6,967,194 B1	11/2005	Matsuo et al.	8,088,605 B2	1/2012	Beaudet et al.	
6,977,250 B2	12/2005	Rodriguez	8,101,209 B2	1/2012	LeGrand et al.	
6,978,945 B2	12/2005	Wong et al.	8,101,773 B2	1/2012	Smith	
7,005,429 B2	2/2006	Dey et al.	8,114,434 B2	2/2012	Sasaki et al.	
7,011,846 B2	3/2006	Shojaei et al.	8,158,614 B2	4/2012	Lambert et al.	
7,018,992 B2	3/2006	Koch et al.	8,182,833 B2	5/2012	Hermsmeyer	
7,030,157 B2	4/2006	Ke et al.	8,202,736 B2	6/2012	Mousa et al.	
RE39,104 E	5/2006	Duclos et al.	8,217,024 B2	7/2012	Ahmed et al.	
7,074,779 B2	7/2006	Sue et al.	8,222,008 B2	7/2012	Thoene	
7,083,590 B1	8/2006	Bunt et al.	8,227,454 B2	7/2012	Hill et al.	
7,091,213 B2	8/2006	Metcalf, III et al.	8,227,509 B2	7/2012	Castro et al.	
7,101,342 B1	9/2006	Caillouette	8,241,664 B2	8/2012	Dudley et al.	
7,135,190 B2	11/2006	Piao et al.	8,247,393 B2	8/2012	Ahmed et al.	
7,163,681 B2	1/2007	Giles-Komar	8,273,730 B2	9/2012	Fernandez et al.	
7,163,699 B2	1/2007	Besse	8,287,888 B2	10/2012	Song et al.	
7,179,799 B2	2/2007	Hill et al.	8,329,680 B2	12/2012	Evans et al.	
7,196,074 B2	3/2007	Blye et al.	8,349,820 B2	1/2013	Zeun et al.	
7,198,801 B2	4/2007	Carrara et al.	8,420,111 B2	4/2013	Hermsmeyer	
7,226,910 B2	6/2007	Wilson et al.	8,435,561 B2	5/2013	Besins et al.	
7,247,625 B2	7/2007	Zhang et al.	8,658,628 B2	2/2014	Baucom	
7,250,446 B2	7/2007	Sangita et al.	8,663,681 B2	3/2014	Ahmed et al.	
7,267,829 B2	9/2007	Kirby et al.	2001/0005728 A1	6/2001	Guittard et al.	
7,300,926 B2	11/2007	Prokai et al.	2001/0021816 A1	9/2001	Caillouette	
7,303,763 B2	12/2007	Ho	2001/0027189 A1	10/2001	Bennink et al.	
7,317,037 B2	1/2008	Fensome et al.	2001/0029357 A1	10/2001	Bunt et al.	
7,329,654 B2	2/2008	Kanojia et al.	2001/0031747 A1	10/2001	DeZiegler et al.	
7,335,650 B2	2/2008	Potter et al.	2001/0034340 A1	10/2001	Pickar	
7,374,779 B2	5/2008	Chen et al.	2001/0056068 A1	12/2001	Chwalisz et al.	
7,378,404 B2	5/2008	Peters	2002/0012710 A1	1/2002	Lansky	
7,387,789 B2	6/2008	Klose et al.	2002/0026158 A1	2/2002	Rathbone et al.	
7,388,006 B2	6/2008	Schmees et al.	2002/0028788 A1	3/2002	Bunt et al.	
7,414,043 B2	8/2008	Kosemund et al.	2002/0058648 A1	5/2002	Hammerly	
7,427,413 B2	9/2008	Savoir et al.	2002/0058926 A1	5/2002	Rathbone et al.	
7,427,609 B2	9/2008	Leonard	2002/0076441 A1	6/2002	Shih et al.	
7,429,576 B2	9/2008	Labrie	2002/0102308 A1	8/2002	Wei et al.	
7,431,941 B2	10/2008	Besins et al.	2002/0107230 A1	8/2002	Waldon et al.	
7,459,445 B2	12/2008	Hill et al.	2002/0114803 A1	8/2002	Deaver et al.	
			2002/0132801 A1	9/2002	Heil et al.	
			2002/0137749 A1	9/2002	Levinson et al.	
			2002/0151530 A1	10/2002	Leonard et al.	
			2002/0156394 A1	10/2002	Mehrotra et al.	

US 8,846,649 B2

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(56)

References Cited**U.S. PATENT DOCUMENTS**

2002/0169150 A1	11/2002	Pickar	2005/0101579 A1	5/2005	Shippen
2002/0173510 A1	11/2002	Levinson et al.	2005/0113350 A1	5/2005	Duesterberg et al.
2002/0193356 A1	12/2002	Van Beek et al.	2005/0118272 A1	6/2005	Besse et al.
2003/0004145 A1	1/2003	Leonard	2005/0153946 A1	7/2005	Hirsh et al.
2003/0007994 A1	1/2003	Bunt et al.	2005/0164977 A1	7/2005	Coelingh Bennink
2003/0049307 A1	3/2003	Gyurik	2005/0182105 A1	8/2005	Nirschl et al.
2003/0064097 A1	4/2003	Patel et al.	2005/0187267 A1	8/2005	Hamann et al.
2003/0072760 A1	4/2003	Sirbasku	2005/0192253 A1	9/2005	Salvati et al.
2003/0073248 A1	4/2003	Roth et al.	2005/0192310 A1	9/2005	Gavai et al.
2003/0073673 A1	4/2003	Hesch	2005/0207990 A1	9/2005	Funke et al.
2003/0077297 A1	4/2003	Chen et al.	2005/0214384 A1	9/2005	Juturu et al.
2003/0078245 A1	4/2003	Bennink et al.	2005/0220825 A1	10/2005	Funke et al.
2003/0091640 A1	5/2003	Ramanathan et al.	2005/0222106 A1	10/2005	Bracht
2003/0092691 A1	5/2003	Besse et al.	2005/0244522 A1	11/2005	Carrara et al.
2003/0096012 A1	5/2003	Besse et al.	2005/0245902 A1	11/2005	Cornish et al.
2003/0104048 A1	6/2003	Patel et al.	2005/0250746 A1	11/2005	Iammateo
2003/0114420 A1	6/2003	Salvati et al.	2005/0250750 A1	11/2005	Cummings et al.
2003/0114430 A1	6/2003	MacLeod et al.	2005/0250753 A1	11/2005	Fink et al.
2003/0124182 A1	7/2003	Shojaei et al.	2005/0256028 A1	11/2005	Yun et al.
2003/0124191 A1	7/2003	Besse et al.	2005/0266078 A1	12/2005	Jorda et al.
2003/0130558 A1	7/2003	Massara et al.	2005/0271598 A1	12/2005	Frieman et al.
2003/0144258 A1	7/2003	Heil et al.	2005/0272712 A1	12/2005	Grubb et al.
2003/0157157 A1	8/2003	Luo et al.	2006/0014728 A1	1/2006	Chwalisz et al.
2003/0166509 A1	9/2003	Edwards et al.	2006/0018937 A1	1/2006	Friedman et al.
2003/0180352 A1	9/2003	Patel et al.	2006/0019978 A1	1/2006	Balog
2003/0181353 A1	9/2003	Nyce	2006/0020002 A1	1/2006	Salvati et al.
2003/0181728 A1	9/2003	Salvati et al.	2006/0030615 A1	2/2006	Fensome et al.
2003/0191096 A1	10/2003	Leonard et al.	2006/0034889 A1	2/2006	Jo et al.
2003/0195177 A1	10/2003	Leonard et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2003/0215496 A1	11/2003	Patel et al.	2006/0052341 A1	3/2006	Cornish et al.
2003/0220297 A1	11/2003	Berstein et al.	2006/0069031 A1	3/2006	Loumaye
2003/0224057 A1	12/2003	Martin-Letellier et al.	2006/0083778 A1	4/2006	Allison et al.
2003/0224059 A1	12/2003	Lerner et al.	2006/0089337 A1	4/2006	Casper et al.
2003/0225050 A1	12/2003	Grawe et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2003/0228686 A1	12/2003	Klausner et al.	2006/0106004 A1	5/2006	Brody et al.
2003/0229057 A1	12/2003	Caubel et al.	2006/0110415 A1	5/2006	Gupta
2004/0009960 A1	1/2004	Heil et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0034001 A1	2/2004	Karara	2006/0121626 A1	6/2006	Imrich
2004/0037881 A1	2/2004	Guittard et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2004/0043943 A1	3/2004	Guittard et al.	2006/0135619 A1	6/2006	Kick et al.
2004/0044080 A1	3/2004	Place et al.	2006/0194775 A1	8/2006	Tofovic et al.
2004/0052824 A1	3/2004	Chacra-Vernet et al.	2006/0204557 A1	9/2006	Gupta et al.
2004/0073024 A1	4/2004	Metcalf, III et al.	2006/0235037 A1	10/2006	Purandare et al.
2004/0077605 A1	4/2004	Salvati et al.	2006/0240111 A1	10/2006	Fernandez et al.
2004/0077606 A1	4/2004	Salvati et al.	2006/0247216 A1	11/2006	Haj-Yehia
2004/0087548 A1	5/2004	Salvati et al.	2006/025049 A1	11/2006	Shuler et al.
2004/0089308 A1	5/2004	Welch	2006/0257472 A1	11/2006	Neilsen
2004/0092583 A1	5/2004	Shanahan-Prendergast	2006/0275360 A1	12/2006	Ahmed et al.
2004/0097468 A1	5/2004	Wimalawansa	2006/0280771 A1	12/2006	Groenewegen et al.
2004/0101557 A1	5/2004	Gibson et al.	2006/0280797 A1	12/2006	Shoichet et al.
2004/0106542 A1	6/2004	Deaver et al.	2006/0280800 A1	12/2006	Nagi et al.
2004/0131670 A1	7/2004	Gao	2007/0004693 A1	1/2007	Woolfson et al.
2004/0142012 A1	7/2004	Bunt et al.	2007/0004694 A1	1/2007	Woolfson et al.
2004/0146894 A1	7/2004	Warrington et al.	2007/0021360 A1	1/2007	Nyce et al.
2004/0176324 A1	9/2004	Salvati et al.	2007/0027201 A1	2/2007	McComas et al.
2004/0176336 A1	9/2004	Rodriguez	2007/0031491 A1	2/2007	Levine et al.
2004/0185104 A1	9/2004	Piao et al.	2007/0042038 A1	2/2007	Besse
2004/0191276 A1	9/2004	Muni	2007/0060589 A1	3/2007	Purandare et al.
2004/0198706 A1	10/2004	Carrara	2007/0066628 A1	3/2007	Zhang et al.
2004/0213744 A1	10/2004	Lulla et al.	2007/0066637 A1	3/2007	Zhang et al.
2004/0234606 A1	11/2004	Levine et al.	2007/0066675 A1	3/2007	Zhang et al.
2004/0253319 A1	12/2004	Netke et al.	2007/0088029 A1	4/2007	Balog et al.
2004/0259817 A1	12/2004	Waldon et al.	2007/0093548 A1	4/2007	Diffendal et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2007/0116729 A1	5/2007	Palepu
2005/0004088 A1	1/2005	Hesch	2007/0116829 A1	5/2007	Prakash et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2007/0178166 A1	8/2007	Bernstein et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2007/0184558 A1	8/2007	Roth et al.
2005/0021009 A1	1/2005	Massara et al.	2007/0191319 A1	8/2007	Ke et al.
2005/0025833 A1	2/2005	Aschkenasy et al.	2007/0196433 A1	8/2007	Ron et al.
2005/0031651 A1	2/2005	Gervais et al.	2007/0207225 A1	9/2007	Squadrito
2005/0042173 A1	2/2005	Besse et al.	2007/0225281 A1	9/2007	Zhang et al.
2005/0042268 A1	2/2005	Aschkenasy et al.	2007/0238713 A1	10/2007	Gast et al.
2005/0048116 A1	3/2005	Straub et al.	2007/0243229 A1	10/2007	Smith et al.
2005/0079138 A1	4/2005	Chickering, III et al.	2007/0264309 A1	11/2007	Chollet et al.
2005/0085453 A1	4/2005	Govindarajan	2007/0264345 A1	11/2007	Eros et al.
			2007/0264349 A1	11/2007	Lee et al.
			2007/0286819 A1	12/2007	DeVries et al.
			2007/0287789 A1	12/2007	Jones et al.
			2007/0292387 A1	12/2007	Jon et al.

US 8,846,649 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2008/0026035 A1	1/2008	Chollet et al.	2011/0135719 A1	6/2011	Besins et al.	
2008/0026062 A1	1/2008	Farr et al.	2011/0182997 A1	7/2011	Lewis et al.	
2008/0038350 A1	2/2008	Gerecke et al.	2011/0195114 A1	8/2011	Carrara et al.	
2008/0085877 A1	4/2008	Bortz	2011/0195944 A1	8/2011	Mura et al.	
2008/0095838 A1	4/2008	Abou Chakra-Vernet	2011/0217341 A1	9/2011	Sah	
2008/0113953 A1	5/2008	De Vries et al.	2011/0250274 A1	10/2011	Shaked et al.	
2008/0114050 A1	5/2008	Fensome et al.	2011/0256092 A1	10/2011	Phiasivongsa et al.	
2008/0119537 A1	5/2008	Zhang et al.	2011/0262494 A1	10/2011	Achleitner et al.	
2008/0125402 A1	5/2008	Diliberti et al.	2011/0268665 A1	11/2011	Tamarkin et al.	
2008/0138379 A1	6/2008	Jennings-Spring	2011/0293720 A1	12/2011	General et al.	
2008/0145423 A1	6/2008	Khan et al.	2011/0311592 A1	12/2011	Birbara	
2008/0175814 A1	7/2008	Phiasivongsa et al.	2011/0312927 A1	12/2011	Nachaegari et al.	
2008/0188829 A1	8/2008	Creasy	2011/0312928 A1	12/2011	Nachaegari et al.	
2008/0206161 A1	8/2008	Tamarkin et al.	2012/0009276 A1	1/2012	De Groot	
2008/0220069 A1	9/2008	Allison	2012/0015350 A1	1/2012	Nabatiyan et al.	
2008/0234199 A1	9/2008	Katamreddym et al.	2012/0045532 A1	2/2012	Cohen	
2008/0255078 A1	10/2008	Katamreddym et al.	2012/0269878 A2	2/2012	Cantor et al.	
2008/0255089 A1	10/2008	Katamreddym et al.	2012/0052077 A1	3/2012	Truitt et al.	
2008/0299220 A1	12/2008	Tamarkin et al.	2012/0128625 A1	5/2012	Shalwitz et al.	
2008/0306036 A1	12/2008	Katamreddy et al.	2012/0128777 A1	5/2012	Keck et al.	
2008/0312197 A1	12/2008	Rodriguez	2012/0149748 A1	6/2012	Shanler et al.	
2008/0312198 A1	12/2008	Rodriguez	2012/0269721 A1	10/2012	Weng et al.	
2008/0319078 A1	12/2008	Katamreddym et al.	2012/0283671 A1	11/2012	Shibata et al.	
2009/0053294 A1	2/2009	Prendergast	2013/0022674 A1	1/2013	Dudley et al.	
2009/0060982 A1	3/2009	Ron et al.	2013/0029947 A1	1/2013	Nachaegari et al.	
2009/0068118 A1	3/2009	Eini et al.	2013/0129818 A1	5/2013	Bernick et al.	
2009/0081278 A1	3/2009	De Graaff et al.	FOREIGN PATENT DOCUMENTS			
2009/0081303 A1	3/2009	Savoir et al.	EP	0275716 A1	7/1988	
2009/0092656 A1	4/2009	Klamerus et al.	EP	0622075 A1	11/1994	
2009/0099106 A1	4/2009	Phiasivongsa et al.	EP	0785211 A1	1/1996	
2009/0131385 A1	5/2009	Voskuhl	EP	0811381 A1	6/1997	
2009/0137478 A1	5/2009	Bernstein et al.	EP	0785212 A1	7/1997	
2009/0137538 A1	5/2009	Klamerus et al.	EP	1094781 B1	7/2008	
2009/0143344 A1	6/2009	Chang	EP	2191833 A1	6/2010	
2009/0181088 A1	7/2009	Song et al.	GB	1589946 A1	2/1921	
2009/0214474 A1	8/2009	Jennings	GB	452238 A	8/1936	
2009/0227025 A1	9/2009	Nichols et al.	GB	720561 A	12/1954	
2009/0232897 A1	9/2009	Sahoo et al.	GB	848881 A	9/1960	
2009/0258096 A1	10/2009	Cohen	GB	874368 A	8/1961	
2009/0264395 A1	10/2009	Creasy et al.	IN	216026 A	3/2008	
2009/0269403 A1	10/2009	Shaked et al.	IN	2005KO00053 A	9/2009	
2009/0285772 A1	11/2009	Phiasivongsa et al.	WO	244217 A	11/2010	
2009/0318558 A1	12/2009	Kim et al.	WO	9011064 A1	10/1990	
2009/0325916 A1	12/2009	Zhang et al.	WO	9317686 A1	9/1993	
2010/0028360 A1	2/2010	Atwood	WO	9422426 A1	10/1994	
2010/0040671 A1	2/2010	Ahmed et al.	WO	9530409 A1	11/1995	
2010/0048523 A1	2/2010	Bachman et al.	WO	9609826 A2	4/1996	
2010/0074959 A1	3/2010	Hansom et al.	WO	9630000 A1	10/1996	
2010/0086599 A1	4/2010	Huemel et al.	WO	9705491	2/1997	
2010/0092568 A1	4/2010	Lerner et al.	WO	9743989 A1	11/1997	
2010/0105071 A1	4/2010	Laufer et al.	WO	9810293 A1	3/1998	
2010/0129320 A1	5/2010	Phiasivongsa et al.	WO	9832465 A1	7/1998	
2010/0136105 A1	6/2010	Chen et al.	WO	9851280 A1	11/1998	
2010/0137265 A1	6/2010	Leonard	WO	9932072	7/1999	
2010/0137271 A1	6/2010	Chen et al.	WO	9939700 A1	8/1999	
2010/0152144 A1	6/2010	Hermsmeyer	WO	9942109 A1	8/1999	
2010/0168228 A1	7/2010	Bose et al.	WO	9943304	9/1999	
2010/0183723 A1	7/2010	Laurent-Applegate	WO	9948477 A1	9/1999	
2010/0184736 A1	7/2010	Coelingh Bennink et al.	WO	9953910 A2	10/1999	
2010/0190758 A1	7/2010	Fauser et al.	WO	9963974 A2	12/1999	
2010/0240626 A1	9/2010	Kulkarni et al.	WO	0001351 A1	1/2000	
2010/0247632 A1	9/2010	Dong et al.	WO	0006175 A1	2/2000	
2010/0255085 A1	10/2010	Liu et al.	WO	0038659 A1	7/2000	
2010/0303825 A9	12/2010	Sirbasku et al.	WO	0045795 A2	8/2000	
2010/0312137 A1	12/2010	Gilmour et al.	WO	0050007 A1	8/2000	
2010/0316724 A1	12/2010	Whitfield et al.	WO	0059577 A1	10/2000	
2010/0330168 A1	12/2010	Gicquel et al.	WO	0137808 A1	11/2000	
2011/0028439 A1	2/2011	Witt-Enderby et al.	WO	0076522 A1	12/2000	
2011/0053845 A1	3/2011	Levine et al.	WO	0154699 A1	8/2001	
2011/0076775 A1	3/2011	Stewart et al.	WO	0160325 A1	8/2001	
2011/0076776 A1	3/2011	Stewart et al.	WO	0207700 A2	2/2002	
2011/0086825 A1	4/2011	Chatroux	WO	0211768 A1	2/2002	
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	WO	0222132 A2	3/2002	
2011/0098631 A1	4/2011	McIntyre et al.	WO	0240008 A2	5/2002	
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	WO	02053131 A1	7/2002	
			WO	02078602 A2	10/2002	
			WO	02078604 A2	10/2002	

US 8,846,649 B2

Page 6

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO 03041718 A1 5/2003
 WO 03041741 A1 5/2003
 WO 03068186 A1 8/2003
 WO 03077923 A1 9/2003
 WO 03082254 A1 10/2003
 WO 03092588 A2 11/2003
 WO 2004017983 A1 3/2004
 WO 2004032897 A2 4/2004
 WO 2004052336 A2 6/2004
 WO 2004054540 A2 7/2004
 WO 2004080413 A2 9/2004
 WO 2005027911 A1 3/2005
 WO 2005030175 A1 4/2005
 WO 2005087194 A1 9/2005
 WO 2005087199 A2 9/2005
 WO 2005105059 A1 11/2005
 WO 2005115335 A1 12/2005
 WO 2005120470 A1 12/2005
 WO 2005120517 A1 12/2005
 WO 2006013369 A2 2/2006
 WO 2006034090 A1 3/2006
 WO 2006036899 A2 4/2006
 WO 2006053172 A2 5/2006
 WO 2006105615 A1 10/2006
 WO 2006113505 A2 10/2006
 WO 2006138686 A1 12/2006
 WO 2006138735 A2 12/2006
 WO 2007045027 A1 4/2007
 WO 2007103294 A2 9/2007
 WO 2007123790 A1 11/2007
 WO 2007124250 A2 11/2007
 WO 2007144151 A1 12/2007
 WO 2008049516 A3 5/2008
 WO 2008152444 A2 12/2008
 WO 2009002542 A1 12/2008
 WO 2009036311 A1 3/2009
 WO 2009040818 4/2009
 WO 2009069006 A2 6/2009
 WO 2009098072 A2 8/2009
 WO 2009133352 A2 11/2009
 WO 2010033188 A2 3/2010
 WO 2011000210 A1 1/2011
 WO 2011073995 A2 6/2011
 WO 2011120084 A1 10/2011
 WO 2011128336 A1 10/2011
 WO 2012009778 A2 1/2012
 WO 2012024361 A1 2/2012
 WO 2013192248 A1 12/2013
 WO 2013192249 A1 12/2013
 WO 2013192250 A1 12/2013
 WO 2013192251 A1 12/2013

OTHER PUBLICATIONS

International Search Report and Written Opinion for related International Application No. PCT/US13/046442 dated Nov. 1, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/046443 dated Oct. 31, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/046444 dated Oct. 31, 2013.
 International Search Report and Written Opinion for related International Application No. PCT/US13/046445 dated Nov. 1, 2013.
 USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.
 USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.
 USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.
 Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.
 Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.

Azure Pharma, Inc., "ELESTRINTM—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages. (Aug. 2009).
 Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER α and ER β ", Endocrinology, 149(10): 4857-4870 (Oct. 2008).
 Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).
 Tahition Noni, "Body Balance Cream," http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/, (undated), 1 page.
 Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.
 Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).
 Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).
 Diramio, "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia-Masters of Science Thesis, 131 pages. (2004). http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1.
 Du, et al. "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 11, (Feb. 2013).
 Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.
 Fuchs, et al., "The Effects of on Estrogen on Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.
 Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.
 Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.
 Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).
 Kincl, et al., "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.
 Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.
 Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Periestrual and Postinsemination Periods in Dairy Cattle," Biol Reprod. 35(2):300-311 (1986). Abstract Only.
 Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.
 NuGest 900TM, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.
 Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, min.sagepub.com. Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
 Panchagnula et al., "Development and Evaluation of an Intrauterine Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," J Pharm Pharmacol. 43(9):609-614 (Sep. 1991). Abstract Only.

US 8,846,649 B2

Page 7

(56)

References Cited

OTHER PUBLICATIONS

- Patel, et al., "Transdermal Drug Delivery System: A Review," www.thepharmajournal.com, vol. 1 No. 4 2012.
- Salole, "The physiochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5 (7):635-648 (1987).
- Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," *American Journal of Public Health*, Published online ahead of print Jul. 18, 2013.
- Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 3, 2014.
- Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," *The American College of Obstetricians and Gynecologists*, vol. 112, No. 5, Nov. 2008.
- Sitruk-Ware, et al., "Oral Micronized Progesterone," *Department of Reproductive Endocrinology*, vol. 36, No. 4, pp. 373-402, Oct. 1987.
- Sitruk-Ware, et al., "Progesterogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," *Menopause: The Journal of the North American Menopause Society*, vol. 9, No. 1, pp. 6-15, 2002.
- Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," *JAMA Internal Medicine* <http://achinte.jamanetwork.com>, Sep. 30, 2013.
- Stanczyk, et al., "Ethynodiol and 17 β -Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment," *Departments of Obstetrics and Gynecology and Preventive Medicine, University of Southern California Keck School of Medicine, Contraception* 87 706-727, (2013).
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230 (Feb. 2004).
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol*, 19:106-121 (2006). http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf.
- Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," *The British Medical Journal*, vol. 280, No. 6217, Mar. 22, 1980.
- Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," *Springer Science+Business Media B.V., Breast Cancer Res Treat* 101:125-134, (2007).
- USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, Vol. 123, No. 1, Jan. 2014, *Obstetrics & Gynecology*.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, *Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div.*, vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, *Pharmaceutica Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.

US 8,846,649 B2

Page 8

(56)

References Cited

OTHER PUBLICATIONS

- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Happgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Sturdy of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, *SciFinder*, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a γ-Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure. Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstatter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas*, *The European Menopause Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffey, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol.Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*,35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.

US 8,846,649 B2

Page 9

(56)

References Cited

OTHER PUBLICATIONS

- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, Natioinal Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmapelidrich.com/catalog/product/sigma/p7556>.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, Cas No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of *Thevetia peruviana* and *Hura crepitans* Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Brazil.
- Gunstone, Frank D, et al., *Vegetable Oils in Food Technology: Composition, Properties and Uses*, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Suplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saftey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot G01L404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.
- Stanczyk, F.Z., Bhavnabii, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, *SciFinder*, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, *SciFinder*, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, *SciFinder Scholar Search*, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , *SciFinder*, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helveticae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC- MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010.

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(56)

References Cited

OTHER PUBLICATIONS

USP Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. SteroidBiochem. Mol. Biol. (2013), Elsevier.

Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.

Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.

Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.

Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.

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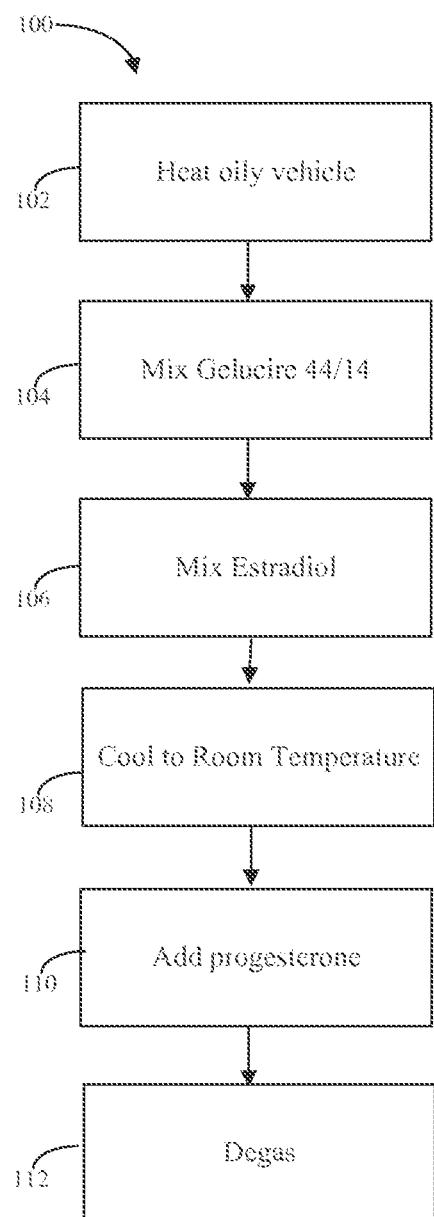
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Fig. 1

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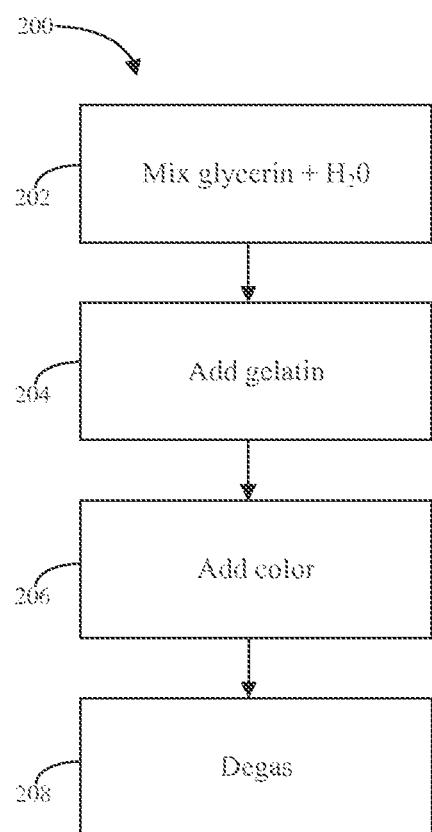


Fig. 2

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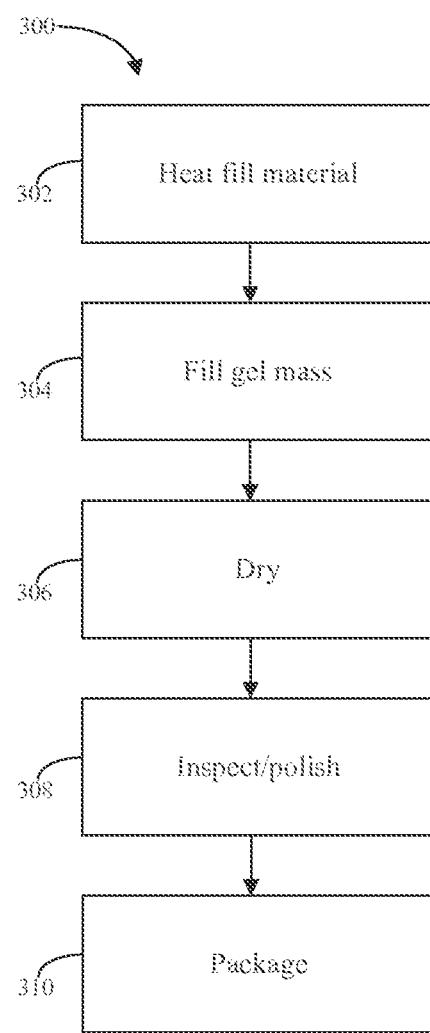


Fig. 3

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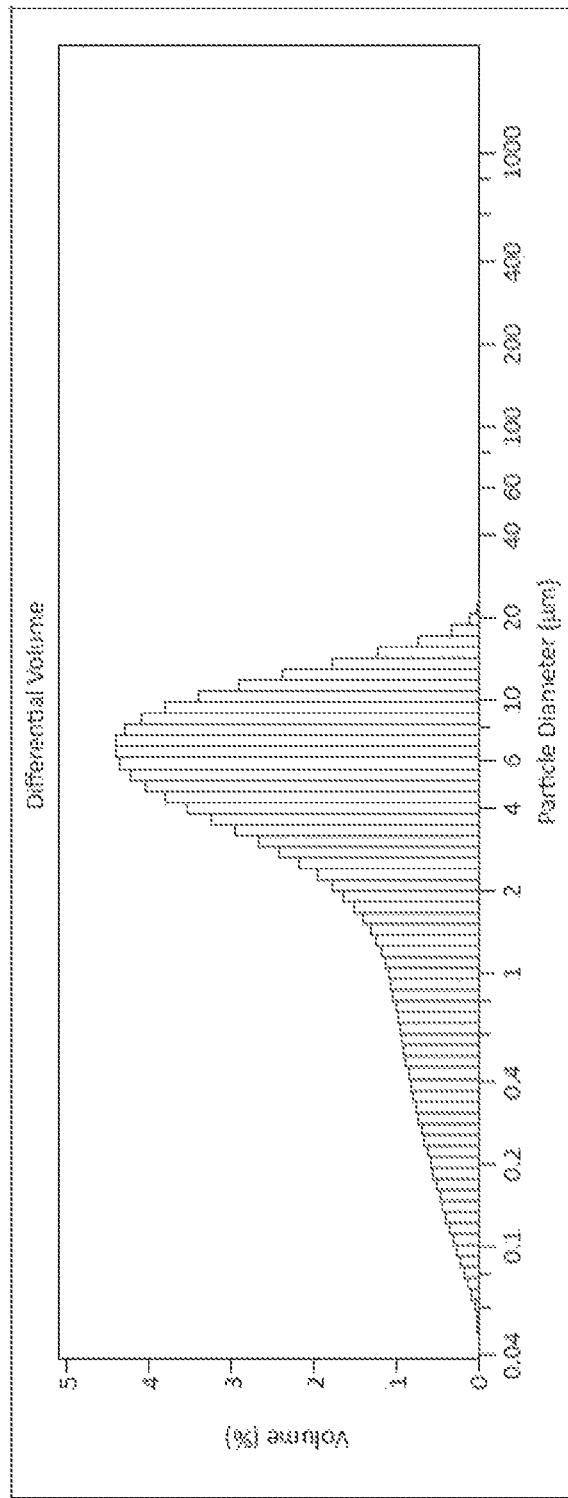


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a non-provisional application of and claims priority to the following U.S. Provisional patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREMPRO (conjugated estrogens/methoxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus methoxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic methoxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

**BRIEF DESCRIPTION OF THE
DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

**DETAILED DESCRIPTION OF THE
ILLUSTRATED EMBODIMENTS**

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

DEFINITIONS

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/

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sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm . The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These

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formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

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Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may

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comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from errone-

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ous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

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EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

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TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

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Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polyisobutene 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride): CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

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12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

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Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
Monocaprylate) (50:50)		
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/ triglycerides of caprylic/capric	322.97	99.38	3.23 kg

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TABLE 8-continued

Ingredient	Mg/Capsule	% w/w	Amount/Batch
acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))			
Total	100	3.25 kg	

5 The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the 20 solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of 30 solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

35 As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

40 Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the 45 estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/Capric Triglyceride)	27.8

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In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF	82.57	57.97	
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF	10.0	70.00	
TOTAL	100.00	700.00	

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to

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40° C.+/-2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w (mg)	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid	394.0	65.67	Carrier	3.94

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TABLE 13-continued

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
(CAPMUL MCM (Medium Chain Mono- and Diglycerides))				
Lauroyl polyoxyl-32- glycerides	6.0	1	Lubricant/ Emulsifier	0.06
(GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) or equivalent)				
Total	600.00	mg	100	6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/ Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) or equivalent) Butylated Hydroxytoluene	3.00	19.50	Suspending Agent
	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10

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mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm, an X75 of 7.442 μm, and an X25 of 1.590 μm. The Beckman Device also yielded that the mean particle size is 4.975 μm, the median particle size is 4.279 μm, the mode particle size is 6.453 μm, and the standard deviation is 3.956 μm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm, an X75 of 17.3 μm, and an X25 of 5.3 μm. The Beckman Device also yielded that the mean particle size is 11.8 μm, the median particle size is 11.04 μm, the mode particle size is 13.6 μm, and the standard deviation is 7.8 μm.

Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF	82.57	577.97	5.78	
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF	10.0	70.00	0.70	
Total:					
		100.00	700.00	7.00	

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono-and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
	Total:		100.000	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono-and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
	Total:		100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The

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mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient tem-

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perature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C.±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules.

Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl

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alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical composition comprising:
solubilized estradiol;
suspended progesterone;
and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and
wherein the solubilizing agent comprises an effective amount of at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. A pharmaceutical composition comprising:
solubilized estradiol;
suspended progesterone; and
a solubilizing agent, the solubilizing agent comprising an effective amount of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid;
wherein the estradiol and the suspended progesterone are present in the solubilizing agent the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

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wherein the estradiol does not precipitate for at least 14 days.

7. The pharmaceutical composition of claim 6, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

8. The pharmaceutical composition of claim 6, wherein the composition is formulated as a gelatin capsule.

9. The pharmaceutical composition of claim 6, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

10. The pharmaceutical composition of claim 6, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

11. A method of treating menopause symptoms of a woman with a uterus comprising:

administering an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent,

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount of at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

12. The method of claim 11, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

13. The method of claim 11, wherein the composition is formulated in a gelatin capsule.

14. The method of claim 11, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

15. The method of claim 11, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,846,649 B2
APPLICATION NO. : 14/099571
DATED : September 30, 2014
INVENTOR(S) : Brian A. Bernick et al.

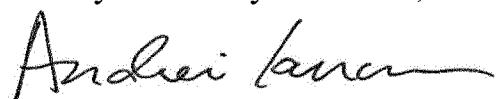
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT D



US008987237B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 8,987,237 B2
(45) **Date of Patent:** *Mar. 24, 2015

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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CPC *A61K 9/7023* (2013.01); *A61K 9/16* (2013.01); *A61K 31/565* (2013.01); *A61K 31/57* (2013.01); *A61K 9/4858* (2013.01)

USPC **514/169; 424/452**

(58) **Field of Classification Search**

CPC A61K 31/56
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Grant et al.
3,198,707 A	8/1965	Nomaine et al.

3,478,070 A	11/1969	Smith et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes
4,012,496 A	3/1977	Schopflin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	Van Der Vies
4,093,709 A	6/1978	Choi
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI 1001367-9 A2	7/2012
CN	102258455 A	11/2011

(Continued)

OTHER PUBLICATIONS

International Search Report and Written Opinion for related International Application No. PCT/US12/066406 dated Jan. 24, 2013.
International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.
International Search Report and Written Opinion for related International Application No. PCT/US13/046442 dated Nov. 1, 2013.
International Search Report and Written Opinion for related International Application No. PCT/US13/046443 dated Oct. 31, 2013.
International Search Report and Written Opinion for related International Application No. PCT/US13/046444 dated Oct. 31, 2013.
International Search Report and Written Opinion for related International Application No. PCT/US13/046445 dated Nov. 1, 2013.
USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.

(Continued)

Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

20 Claims, 4 Drawing Sheets

US 8,987,237 B2

Page 2

(56)	References Cited					
U.S. PATENT DOCUMENTS						
4,237,885 A	12/1980	Wong	5,676,968 A	10/1997	Lipp et al.	
4,310,510 A	1/1982	Sherman et al.	5,677,292 A	10/1997	Li et al.	
4,327,725 A	5/1982	Cortese et al.	5,686,097 A	11/1997	Taskovich et al.	
4,372,951 A	2/1983	Vorys	5,693,335 A	12/1997	Xia et al.	
4,384,096 A	5/1983	Sonnabend	5,694,947 A	12/1997	Lehtinen et al.	
4,393,871 A	7/1983	Vorhauer	5,700,480 A	12/1997	Hille et al.	
4,402,695 A	9/1983	Wong	5,709,844 A	1/1998	Arbeit et al.	
4,423,151 A	12/1983	Baranezuk	5,719,197 A	2/1998	Kanios et al.	
4,449,980 A	5/1984	Millar et al.	5,735,801 A	4/1998	Caillouette	
4,610,687 A	9/1986	Fogwell	5,739,176 A	4/1998	Dunn et al.	
4,629,449 A	12/1986	Wong	5,744,463 A	4/1998	Bair	
4,732,763 A	3/1988	Beck et al.	5,747,058 A	5/1998	Tipton et al.	
4,738,957 A	4/1988	Laurent et al.	5,762,614 A	6/1998	Caillouette	
4,756,907 A	7/1988	Beck et al.	5,770,176 A	6/1998	Nargessi	
4,762,717 A	8/1988	Crowley	5,770,219 A	6/1998	Chiang et al.	
4,788,062 A	11/1988	Gale et al.	5,770,220 A	6/1998	Meconi et al.	
4,816,257 A	3/1989	Buster et al.	5,770,227 A	6/1998	Dong et al.	
4,822,616 A	4/1989	Zimmermann et al.	5,776,495 A	7/1998	Duclos et al.	
4,865,848 A	9/1989	Cheng et al.	5,780,044 A	7/1998	Yewey et al.	
4,900,734 A	2/1990	Maxson et al.	5,780,050 A	7/1998	Jain et al.	
4,906,475 A	3/1990	Kim	5,788,980 A	8/1998	Nabahi	
4,942,158 A	7/1990	Sarpotdar et al.	5,788,984 A	8/1998	Guenther et al.	
4,961,931 A	10/1990	Wong	5,789,442 A	8/1998	Garfield et al.	
5,030,629 A	7/1991	Rajadhyaksha	5,811,416 A	9/1998	Chwalisz	
5,064,654 A	11/1991	Berner et al.	5,811,547 A	9/1998	Nakamichi et al.	
5,108,995 A	4/1992	Casper	5,814,329 A	9/1998	Shah	
5,128,138 A	7/1992	Blank	5,820,878 A	10/1998	Hirano et al.	
5,130,137 A	7/1992	Crowley	5,827,200 A	10/1998	Caillouette	
5,140,021 A	8/1992	Maxson et al.	5,840,327 A	11/1998	Gale et al.	
5,211,952 A	5/1993	Pike et al.	5,843,468 A	12/1998	Burkoth et al.	
5,252,334 A	10/1993	Chiang et al.	5,843,979 A	12/1998	Wille et al.	
5,280,023 A	1/1994	Ehrlich et al.	5,858,394 A	1/1999	Lipp et al.	
5,288,496 A	2/1994	Lewis	5,863,552 A	1/1999	Yue	
5,340,584 A	8/1994	Spicer et al.	5,866,603 A	2/1999	Li et al.	
5,340,585 A	8/1994	Pike et al.	5,882,676 A	3/1999	Lee et al.	
5,340,586 A	8/1994	Pike et al.	5,885,612 A	3/1999	Meconi et al.	
5,362,497 A	11/1994	Yamada et al.	5,888,533 A	3/1999	Dunn	
5,382,573 A	1/1995	Casper	5,891,462 A	4/1999	Carrara	
5,393,528 A	2/1995	Staab	5,891,868 A	4/1999	Cummings et al.	
5,393,529 A	2/1995	Hoffmann et al.	5,898,038 A	4/1999	Yallampalli et al.	
5,419,910 A	5/1995	Lewis	5,902,603 A	5/1999	Chen et al.	
5,468,736 A	11/1995	Hodgen	5,904,931 A	5/1999	Lipp et al.	
5,474,783 A	12/1995	Miranda et al.	5,906,830 A	5/1999	Farinas et al.	
5,480,776 A	1/1996	Dullien	5,912,010 A	6/1999	Wille et al.	
5,514,673 A	5/1996	Heckenmuller et al.	5,916,176 A	6/1999	Caillouette	
5,516,528 A	5/1996	Hughes et al.	RE36,247 E	7/1999	Plunkett et al.	
5,527,534 A	6/1996	Myhling	5,919,477 A	7/1999	Bevan et al.	
5,529,782 A	6/1996	Staab	5,922,349 A	7/1999	Elliesen et al.	
5,538,736 A	7/1996	Hoffmann et al.	5,928,666 A	7/1999	Farinas et al.	
5,543,150 A	8/1996	Bologna et al.	5,942,243 A	8/1999	Shah	
5,547,948 A	8/1996	Barcomb	5,952,000 A	9/1999	Venkateshwaran et al.	
5,556,635 A	9/1996	Istin et al.	5,958,446 A	9/1999	Miranda et al.	
5,565,199 A	10/1996	Page et al.	5,962,445 A	10/1999	Stewart	
5,567,831 A	10/1996	Li	5,968,919 A	10/1999	Samour et al.	
5,569,652 A	10/1996	Beier et al.	5,972,372 A	10/1999	Saleh et al.	
5,580,572 A	12/1996	Mikler et al.	5,985,311 A	11/1999	Cordes et al.	
5,582,592 A	12/1996	Kendrick	5,985,850 A	11/1999	Falk et al.	
5,585,370 A	12/1996	Casper	5,985,861 A	11/1999	Levine et al.	
5,595,759 A	1/1997	Wright et al.	5,989,568 A	11/1999	Breton et al.	
5,595,970 A	1/1997	Garfield et al.	5,993,856 A	11/1999	Ragavan et al.	
5,605,702 A	2/1997	Teillaud et al.	6,001,846 A	12/1999	Edwards et al.	
5,607,691 A	3/1997	Hale et al.	6,007,835 A	12/1999	Bon-Lapillon et al.	
5,607,693 A	3/1997	Bonte et al.	6,010,715 A	1/2000	Wick et al.	
5,609,617 A	3/1997	Shealy et al.	6,013,276 A	1/2000	Math et al.	
5,620,705 A	4/1997	Dong et al.	6,022,562 A	2/2000	Autant et al.	
5,626,866 A	5/1997	Ebert et al.	6,024,974 A	2/2000	Li	
5,629,021 A	5/1997	Wright	6,024,976 A	2/2000	Miranda et al.	
5,633,011 A	5/1997	Dong et al.	6,056,972 A	5/2000	Hermsmeyer	
5,633,242 A	5/1997	Ottel et al.	6,060,077 A	5/2000	Meignant	
5,639,743 A	6/1997	Kaswan et al.	6,068,853 A	5/2000	Giannos et al.	
5,653,983 A	8/1997	Meybeck et al.	6,074,625 A	6/2000	Hawthorne et al.	
5,656,286 A	8/1997	Miranda et al.	6,077,531 A	6/2000	Salin-Drouin	
5,660,839 A	8/1997	Allec et al.	6,080,118 A	6/2000	Blythe	
5,662,927 A	9/1997	Ehrlich et al.	6,083,178 A	7/2000	Caillouette	
5,663,160 A	9/1997	Meybeck et al.	6,086,916 A	7/2000	Agnus et al.	

US 8,987,237 B2

Page 3

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,087,352 A	7/2000	Trout	6,503,896 B1	1/2003	Tanabe et al.	
6,090,404 A	7/2000	Meconi et al.	6,511,969 B1	1/2003	Hermsmeyer	
6,096,338 A	8/2000	Lacy et al.	6,521,250 B2	2/2003	Meconi et al.	
6,106,848 A	8/2000	Preuilh et al.	6,526,980 B1	3/2003	Tracy et al.	
6,117,446 A	9/2000	Place	6,528,094 B1	3/2003	Savoir et al.	
6,117,450 A	9/2000	Dittgen et al.	6,531,149 B1	3/2003	Kirstgen et al.	
6,124,362 A	9/2000	Bradbury et al.	6,537,580 B1	3/2003	Savoir et al.	
6,133,251 A	10/2000	Dittgen et al.	6,538,039 B2	3/2003	Laurent	
6,133,320 A	10/2000	Yallampalli et al.	6,551,611 B2	4/2003	Elliesen et al.	
6,139,868 A	10/2000	Hoffmann	6,555,131 B1	4/2003	Wolff et al.	
6,139,873 A	10/2000	Hughes, Jr. et al.	6,562,367 B1	5/2003	Wolff et al.	
6,149,935 A	11/2000	Chiang et al.	6,562,370 B2	5/2003	Luo et al.	
6,153,216 A	11/2000	Cordes et al.	6,562,790 B2	5/2003	Chein	
6,165,491 A	12/2000	Grasset et al.	6,569,463 B2	5/2003	Patel et al.	
6,165,975 A	12/2000	Adams et al.	6,583,129 B1	6/2003	Mazer et al.	
6,187,323 B1	2/2001	Aiache et al.	6,586,006 B2	7/2003	Roser et al.	
6,187,339 B1	2/2001	de Haan et al.	6,589,549 B2	7/2003	Shih et al.	
6,190,331 B1	2/2001	Caillouette	6,593,317 B1	7/2003	De Ziegler et al.	
6,201,072 B1	3/2001	Rathi et al.	6,599,519 B1	7/2003	Seo et al.	
6,217,886 B1	4/2001	Onyueksel et al.	6,610,652 B2	8/2003	Adams et al.	
6,225,297 B1	5/2001	Stockemann et al.	6,610,670 B2	8/2003	Backensfeld et al.	
6,227,202 B1	5/2001	Matapurkar	6,610,674 B1	8/2003	Schreiber	
6,228,383 B1	5/2001	Hansen et al.	6,635,274 B1	10/2003	Masiz et al.	
6,228,852 B1	5/2001	Shaak	6,638,528 B1	10/2003	Kanios	
6,242,509 B1	6/2001	Berger et al.	6,638,536 B2	10/2003	Savoir et al.	
6,245,811 B1	6/2001	Horrobin et al.	6,645,528 B1	11/2003	Straub et al.	
6,262,115 B1	7/2001	Guitard et al.	6,649,155 B1	11/2003	Dunlop et al.	
6,267,984 B1	7/2001	Beste et al.	6,653,298 B2	11/2003	Potter et al.	
6,274,165 B1	8/2001	Meconi et al.	6,656,929 B1	12/2003	Agnus et al.	
6,277,418 B1	8/2001	Markaverich et al.	6,660,726 B2	12/2003	Hill et al.	
6,283,927 B1	9/2001	Caillouette	6,663,608 B2	12/2003	Rathbone et al.	
6,287,588 B1	9/2001	Shih et al.	6,663,895 B2	12/2003	Savoir et al.	
6,287,693 B1	9/2001	Savoir et al.	6,682,757 B1	1/2004	Wright	
6,294,188 B1	9/2001	Ragavan et al.	6,692,763 B1	2/2004	Cummings et al.	
6,294,192 B1	9/2001	Patel et al.	6,708,822 B1	3/2004	Muni	
6,294,550 B1	9/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.	
6,299,900 B1	10/2001	Reed et al.	6,740,333 B2	5/2004	Beckett et al.	
6,303,132 B1	10/2001	Nelson	6,743,448 B2	6/2004	Kryger	
6,303,588 B1	10/2001	Danielov	6,743,815 B2	6/2004	Huebner et al.	
6,306,841 B1	10/2001	Place et al.	6,747,018 B2	6/2004	Tanabe et al.	
6,306,914 B1	10/2001	Ziegler et al.	6,750,291 B2	6/2004	Kim et al.	
6,309,669 B1	10/2001	Setterstrom et al.	6,756,208 B2	6/2004	Griffin et al.	
6,309,848 B1	10/2001	Howett et al.	6,776,164 B2	8/2004	Bunt et al.	
6,312,703 B1	11/2001	Orthofer	6,787,152 B2	9/2004	Kirby et al.	
6,328,987 B1	12/2001	Marini	6,805,877 B2	10/2004	Massara et al.	
6,342,491 B1	1/2002	Dey et al.	6,809,085 B1	10/2004	Elson et al.	
6,344,211 B1	2/2002	Hille	6,818,226 B2	11/2004	Reed et al.	
6,372,209 B1	4/2002	Chrisope	6,821,524 B2	11/2004	Marini	
6,372,245 B1	4/2002	Bowman et al.	6,841,716 B1	1/2005	Tsutsumi	
6,372,246 B1	4/2002	Wei	6,844,334 B2	1/2005	Hill et al.	
6,387,390 B1	5/2002	Deaver et al.	6,855,703 B1	2/2005	Hill et al.	
6,402,705 B1	6/2002	Caillouette	6,860,859 B2	3/2005	Mehrotra et al.	
6,416,778 B1	7/2002	Ragavan et al.	6,866,865 B2	3/2005	Hsia et al.	
6,420,352 B1	7/2002	Knowles	6,869,969 B2	3/2005	Huebner et al.	
6,423,039 B1	7/2002	Rathbone et al.	6,878,518 B2	4/2005	Whitehead	
6,423,683 B1	7/2002	Heaton et al.	6,901,278 B1	5/2005	Notelovitz	
6,432,438 B1	8/2002	Shukla	6,905,705 B2	6/2005	Palm et al.	
6,436,633 B1	8/2002	Kreider et al.	6,911,211 B2	6/2005	Eini et al.	
6,440,454 B1	8/2002	Santoro et al.	6,911,438 B2	6/2005	Wright	
6,444,224 B1	9/2002	Rathbone et al.	6,923,988 B2	8/2005	Patel et al.	
6,444,234 B1	9/2002	Kirby et al.	6,924,274 B2	8/2005	Lardy et al.	
6,451,300 B1	9/2002	Dunlop et al.	6,932,983 B1	8/2005	Straub et al.	
6,451,339 B2	9/2002	Patel et al.	6,939,558 B2	9/2005	Massara et al.	
6,451,779 B1	9/2002	Hesch	6,943,021 B2	9/2005	Klausner et al.	
6,455,246 B1	9/2002	Howell et al.	6,958,327 B1	10/2005	Hillisch et al.	
6,455,517 B1	9/2002	Tanabe et al.	6,960,337 B2	11/2005	Daniels et al.	
6,465,004 B1	10/2002	Rossi-Montero et al.	6,962,691 B1	11/2005	Lulla et al.	
6,465,005 B1	10/2002	Biali et al.	6,962,908 B2	11/2005	Aloba et al.	
6,465,006 B1	10/2002	Zhang et al.	6,967,194 B1	11/2005	Matsuo et al.	
6,468,526 B2	10/2002	Chrisope	6,974,569 B2	12/2005	Dunlop et al.	
6,469,016 B1	10/2002	Place et al.	6,977,250 B2	12/2005	Rodriguez	
6,472,434 B1	10/2002	Place et al.	6,978,945 B2	12/2005	Wong et al.	
6,479,232 B1	11/2002	Howett et al.	6,995,149 B1	2/2006	Endrikat et al.	
6,495,160 B2	12/2002	Esposito et al.	7,004,321 B1	2/2006	Palm et al.	
6,500,814 B1	12/2002	Hesch	7,005,429 B2	2/2006	Dey et al.	

US 8,987,237 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
7,011,846 B2	3/2006	Shojaei et al.	7,862,552 B2	1/2011	McIntyre et al.	
7,018,992 B2	3/2006	Koch et al.	7,867,990 B2	1/2011	Schultz et al.	
7,030,104 B2	4/2006	Gray et al.	7,871,643 B2	1/2011	Lizio et al.	
7,030,157 B2	4/2006	Ke et al.	7,879,830 B2	2/2011	Wiley	
RE39,104 E	5/2006	Duclos et al.	7,884,093 B2	2/2011	Creasy et al.	
7,074,779 B2	7/2006	Sue et al.	7,939,104 B2	5/2011	Barbera et al.	
7,083,590 B1	8/2006	Bunt et al.	7,943,602 B2	5/2011	Bunschoten et al.	
7,091,213 B2	8/2006	Metcalf, III et al.	7,943,604 B2	5/2011	Coelingh Bennik et al.	
7,094,228 B2	8/2006	Zhang et al.	8,022,053 B2	9/2011	Nickisch et al.	
7,097,853 B1	8/2006	Garbe et al.	8,048,017 B2	11/2011	Hill et al.	
7,101,342 B1	9/2006	Caillouette	8,048,869 B2	11/2011	Welsh et al.	
7,105,573 B2	9/2006	Krajcik et al.	8,063,030 B2	12/2011	Mueller et al.	
7,135,190 B2	11/2006	Piao et al.	8,071,576 B2	12/2011	Ellman	
7,153,522 B1	12/2006	Ikeura et al.	8,071,729 B2	12/2011	Giles-Komar et al.	
7,163,681 B2	1/2007	Giles-Komar	8,075,916 B2	12/2011	Coelingh Bennink et al.	
7,163,699 B2	1/2007	Besse	8,075,917 B2	12/2011	Song et al.	
7,175,850 B2	2/2007	Cevc	8,076,317 B2	12/2011	Chung et al.	
7,179,799 B2	2/2007	Hill et al.	8,076,319 B2	12/2011	Kulmann	
7,196,074 B2	3/2007	Blye et al.	8,080,553 B2	12/2011	Leonard	
7,198,800 B1	4/2007	Ko	8,088,605 B2	1/2012	Keith et al.	
7,198,801 B2	4/2007	Carrara et al.	8,096,940 B2	1/2012	Beaudet et al.	
7,226,910 B2	6/2007	Wilson et al.	8,101,209 B2	1/2012	Josephson et al.	
7,247,625 B2	7/2007	Zhang et al.	8,101,773 B2	1/2012	Legrand et al.	
7,250,446 B2	7/2007	Sangita et al.	8,114,152 B2	1/2012	Smith	
7,267,829 B2	9/2007	Kirby et al.	8,114,434 B2	1/2012	Furst	
7,300,926 B2	11/2007	Prokai et al.	8,114,442 B2	1/2012	Sasaki et al.	
7,303,763 B2	12/2007	Ho	8,119,741 B2	1/2012	Tucker et al.	
7,317,037 B2	1/2008	Fensome et al.	8,124,118 B2	1/2012	Pavlin	
7,329,654 B2	2/2008	Kanojia et al.	8,124,595 B2	1/2012	Lennernaes et al.	
7,335,650 B2	2/2008	Potter et al.	8,147,561 B2	1/2012	Boissonneault	
7,374,779 B2	5/2008	Chen et al.	8,148,546 B2	1/2012	Binmoeller	
7,378,404 B2	5/2008	Peters	8,158,613 B2	1/2012	Schuster et al.	
7,381,427 B2	6/2008	Ancira et al.	8,158,614 B2	1/2012	Staniforth et al.	
7,387,789 B2	6/2008	Klose et al.	8,163,722 B2	1/2012	Lambert et al.	
7,388,006 B2	6/2008	Schmees et al.	8,177,449 B2	1/2012	Savoir et al.	
7,414,043 B2	8/2008	Kosemund et al.	8,182,833 B2	1/2012	Bayly et al.	
7,427,413 B2	9/2008	Savoir et al.	8,187,615 B2	1/2012	Hermsmeyer	
7,427,609 B2	9/2008	Leonard	8,195,403 B2	1/2012	Friedman	
7,429,576 B2	9/2008	Labrie	8,202,736 B2	1/2012	Ishikawa et al.	
7,431,941 B2	10/2008	Besins et al.	8,217,024 B2	1/2012	Mousa et al.	
7,456,159 B2	11/2008	Houze et al.	8,221,785 B2	1/2012	Ahmed et al.	
7,459,445 B2	12/2008	Hill et al.	8,222,008 B2	1/2012	Chien	
7,465,587 B2	12/2008	Imrich	8,222,237 B2	1/2012	Thoene	
7,470,433 B2	12/2008	Carrara et al.	8,227,454 B2	1/2012	Nickisch et al.	
7,485,666 B2	2/2009	Villanueva et al.	8,227,509 B2	1/2012	Hill et al.	
7,497,855 B2	3/2009	Ausiello et al.	8,241,664 B2	1/2012	Castro et al.	
7,498,303 B2	3/2009	Arnold et al.	8,247,393 B2	1/2012	Dudley et al.	
7,534,765 B2	5/2009	Gregg et al.	8,257,724 B2	1/2012	Ahmed et al.	
7,534,780 B2	5/2009	Wyrwa et al.	8,257,725 B2	1/2012	Cromack et al.	
7,550,142 B2	6/2009	Giles-Komar et al.	8,268,352 B2	1/2012	Vaya et al.	
7,563,565 B1	7/2009	Matsuo et al.	8,268,806 B2	1/2012	Labrie	
7,569,274 B2	8/2009	Besse et al.	8,268,878 B2	1/2012	Armer et al.	
7,572,779 B2	8/2009	Aloba et al.	8,273,730 B2	1/2012	Fernandez et al.	
7,572,780 B2	8/2009	Hermsmeyer	8,287,888 B2	1/2012	Song et al.	
7,589,082 B2	9/2009	Savoir et al.	8,288,366 B2	1/2012	Chochinov et al.	
7,671,027 B2	3/2010	Loumaye	8,318,898 B2	1/2012	Fasel et al.	
7,674,783 B2	3/2010	Hermsmeyer	8,324,193 B2	1/2012	Lee-Sepick et al.	
7,687,281 B2	3/2010	Roth et al.	8,329,680 B2	1/2012	Evans et al.	
7,687,485 B2	3/2010	Levinson et al.	8,337,814 B2	1/2012	Osbakken et al.	
7,694,683 B2	4/2010	Callister et al.	8,344,007 B2	1/2013	Tang et al.	
7,704,983 B1	4/2010	Hodgen et al.	8,349,820 B2	1/2013	Zeun et al.	
7,727,720 B2	6/2010	Dhallan	8,353,863 B2	1/2013	Imran	
7,732,408 B2	6/2010	Josephson et al.	8,357,723 B2	1/2013	Satyam	
7,749,989 B2	7/2010	Hill et al.	8,361,995 B2	1/2013	Schramm	
7,767,656 B2	8/2010	Shoichet et al.	8,362,091 B2	1/2013	Tamarkin et al.	
7,799,769 B2	9/2010	White et al.	8,372,424 B2	2/2013	Berry et al.	
7,815,936 B2	10/2010	Hasenzahl et al.	8,372,806 B2	2/2013	Boehler et al.	
7,815,949 B2	10/2010	Cohen	8,377,482 B2	2/2013	Laurie et al.	
7,829,115 B2	11/2010	Besins et al.	8,377,994 B2	2/2013	Gray et al.	
7,829,116 B2	11/2010	Griswold et al.	8,394,759 B2	3/2013	Barathur et al.	
RE42,012 E	12/2010	Deaver et al.	8,415,332 B2	4/2013	Diliberti et al.	
7,850,992 B2	12/2010	Kim et al.	8,420,111 B2	4/2013	Hermsmeyer	
7,854,753 B2	12/2010	Kraft et al.	8,435,561 B2	5/2013	Besins et al.	
7,858,607 B2	12/2010	Mamchur	8,435,972 B2	5/2013	Stein et al.	
RE42,072 E	1/2011	Deaver et al.	8,449,879 B2	5/2013	Laurent-Applegate et al.	
			8,450,108 B2	5/2013	Boyce	

US 8,987,237 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
8,454,945 B2	6/2013 McCook et al.	2002/0169205 A1	11/2002 Chwalisz et al.			
8,455,468 B2	6/2013 Hoffman et al.	2002/0173510 A1	11/2002 Levinson et al.			
8,461,138 B2	6/2013 Boissonneault	2002/0193356 A1	12/2002 Van Beek et al.			
8,476,252 B2	7/2013 Achleitner et al.	2002/0193758 A1	12/2002 Sandberg			
8,481,488 B2	7/2013 Carter	2002/0197286 A1	12/2002 Brandman et al.			
8,486,374 B2	7/2013 Tamarkin et al.	2003/0003139 A1	1/2003 Lipp et al.			
8,486,442 B2	7/2013 Matsushita et al.	2003/0004145 A1	1/2003 Leonard			
8,492,368 B2	7/2013 Vanlandingham et al.	2003/0007994 A1	1/2003 Bunt et al.			
8,507,467 B2	8/2013 Matsui et al.	2003/0027772 A1	2/2003 Breton			
8,512,693 B2	8/2013 Capito et al.	2003/0044453 A1	3/2003 Dittgen et al.			
8,512,754 B2	8/2013 Needham	2003/0049307 A1	3/2003 Gyurik			
8,518,376 B2	8/2013 Tamarkin et al.	2003/0064097 A1	4/2003 Patel et al.			
8,536,159 B2	9/2013 Li et al.	2003/0072760 A1	4/2003 Sirkasku			
8,540,967 B2	9/2013 Barrett et al.	2003/0073248 A1	4/2003 Roth et al.			
8,541,400 B2	9/2013 Johnsson et al.	2003/0073673 A1	4/2003 Hesch			
8,551,462 B2	10/2013 Goldstein et al.	2003/0077297 A1 *	4/2003 Chen et al. 424/400			
8,557,281 B2	10/2013 Halliday et al.	2003/0078245 A1	4/2003 Bennink et al.			
8,568,374 B2	10/2013 De Graaff et al.	2003/0091620 A1	5/2003 Fikstad et al.			
8,591,951 B2	11/2013 Kohn et al.	2003/0091640 A1	5/2003 Ramanathan et al.			
8,613,951 B2	12/2013 Zale et al.	2003/0092691 A1	5/2003 Besse et al.			
8,633,178 B2	1/2014 Bernick et al.	2003/0096012 A1	5/2003 Besse et al.			
8,633,180 B2	1/2014 Li et al.	2003/0104048 A1	6/2003 Patel et al.			
8,636,787 B2	1/2014 Sabaria	2003/0109507 A1	6/2003 Franke et al.			
8,636,982 B2	1/2014 Tamarkin et al.	2003/0113268 A1	6/2003 Buenafae et al.			
8,653,129 B2	2/2014 Fein et al.	2003/0114420 A1	6/2003 Salvati et al.			
8,658,627 B2	2/2014 Voskuhl	2003/0114430 A1	6/2003 MacLeod et al.			
8,658,628 B2	2/2014 Baucom	2003/0124182 A1	7/2003 Shojaei et al.			
8,663,681 B2	3/2014 Ahmed et al.	2003/0124191 A1	7/2003 Besse et al.			
8,663,692 B1	3/2014 Mueller et al.	2003/0130558 A1	7/2003 Massara et al.			
8,663,703 B2	3/2014 Lerner et al.	2003/0144258 A1	7/2003 Heil et al.			
8,664,207 B2	3/2014 Li et al.	2003/0157157 A1	8/2003 Luo et al.			
8,669,293 B2	3/2014 Levy et al.	2003/0166509 A1	9/2003 Edwards et al.			
8,679,552 B2	3/2014 Guthery	2003/0170295 A1	9/2003 Kim et al.			
8,697,127 B2	4/2014 Sah	2003/0175329 A1	9/2003 Azarnoff et al.			
8,697,710 B2	4/2014 Li et al.	2003/0175333 A1	9/2003 Shefer et al.			
8,703,105 B2	4/2014 Tamarkin et al.	2003/0180352 A1	9/2003 Patel et al.			
8,709,385 B2	4/2014 Tamarkin et al.	2003/0181353 A1	9/2003 Nyce			
8,709,451 B2	4/2014 Nam et al.	2003/0181728 A1	9/2003 Salvati et al.			
8,715,735 B2	5/2014 Funke et al.	2003/0191096 A1	10/2003 Leonard et al.			
8,721,331 B2	5/2014 Raguprasad	2003/0195177 A1	10/2003 Leonard et al.			
8,722,021 B2	5/2014 Friedman et al.	2003/0215496 A1	11/2003 Patel et al.			
8,734,846 B2	5/2014 Ali et al.	2003/0219402 A1	11/2003 Rutter			
8,735,381 B2	5/2014 Podolski	2003/0220297 A1	11/2003 Berstein et al.			
8,741,336 B2	6/2014 Dipierro et al.	2003/0224057 A1	12/2003 Martin-Letellier et al.			
8,741,373 B2	6/2014 Bromley et al.	2003/0224059 A1	12/2003 Lerner et al.			
8,753,661 B2	6/2014 Steinmuller-Nethl et al.	2003/0225047 A1	12/2003 Caubel et al.			
8,784,882 B2	7/2014 Mattern	2003/0225048 A1	12/2003 Caubel et al.			
2001/0005728 A1	6/2001 Guittard et al.	2003/0225050 A1	12/2003 Grawe et al.			
2001/0009673 A1	7/2001 Lipp et al.	2003/0228686 A1	12/2003 Klausner et al.			
2001/0021816 A1	9/2001 Caillouette	2003/0229057 A1	12/2003 Caubel et al.			
2001/0023261 A1	9/2001 Ryoo et al.	2003/0235596 A1	12/2003 Gao et al.			
2001/0027189 A1	10/2001 Bennink et al.	2003/0236236 A1 *	12/2003 Chen et al. 514/171			
2001/0029357 A1	10/2001 Bunt et al.	2004/0009960 A1	1/2004 Heil et al.			
2001/0031747 A1	10/2001 Deziegler et al.	2004/0022820 A1	2/2004 Anderson			
2001/0034340 A1	10/2001 Pickar	2004/0034001 A1	2/2004 Karara			
2001/0053383 A1	12/2001 Miranda et al.	2004/0037881 A1	2/2004 Guittard et al.			
2001/0056068 A1	12/2001 Chwalisz et al.	2004/0039356 A1	2/2004 Maki et al.			
2002/0012710 A1	1/2002 Lansky	2004/0040343 A1	3/2004 Schlyter et al.			
2002/0026158 A1	2/2002 Rathbone et al.	2004/0043943 A1	3/2004 Guittard et al.			
2002/0028788 A1	3/2002 Bunt et al.	2004/0044080 A1	3/2004 Place et al.			
2002/0035070 A1	3/2002 Gardlik et al.	2004/0048900 A1	3/2004 Flood			
2002/0058648 A1	5/2002 Hammerly	2004/0052824 A1	3/2004 Chacra-Vernet et al.			
2002/0058926 A1	5/2002 Rathbone et al.	2004/0073024 A1	4/2004 Metcalf, III et al.			
2002/0076441 A1	6/2002 Shih et al.	2004/0077605 A1	4/2004 Salvati et al.			
2002/0102308 A1	8/2002 Wei et al.	2004/0077606 A1	4/2004 Salvati et al.			
2002/0107230 A1	8/2002 Waldon et al.	2004/0087548 A1	5/2004 Salvati et al.			
2002/0114803 A1	8/2002 Deaver et al.	2004/0087564 A1	5/2004 Wright et al.			
2002/0119174 A1	8/2002 Gardlik et al.	2004/0089308 A1	5/2004 Welch			
2002/0119198 A1	8/2002 Gao et al.	2004/0092494 A9	5/2004 Dudley			
2002/0132801 A1	9/2002 Heil et al.	2004/0092583 A1	5/2004 Shanahan-Prendergast			
2002/0137749 A1	9/2002 Levinson et al.	2004/0097468 A1	5/2004 Wimalawansa			
2002/0142017 A1	10/2002 Simonnet et al.	2004/0101557 A1	5/2004 Gibson et al.			
2002/0151530 A1	10/2002 Leonard et al.	2004/0106542 A1	6/2004 Deaver et al.			
2002/0156394 A1	10/2002 Mehrotra et al.	2004/0131670 A1	6/2004 Masini-Etevel et al.			
2002/0169150 A1	11/2002 Pickar	2004/0138103 A1	7/2004 Gao			
		2004/0142012 A1	7/2004 Patt			
		2004/0146539 A1	7/2004 Bunt et al.			
		2004/0146894 A1	7/2004 Gupta			
		2004/0146894 A1	7/2004 Warrington et al.			

US 8,987,237 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2004/0161435 A1	8/2004	Gupta	2006/0069031 A1	3/2006	Loumaye
2004/0176324 A1	9/2004	Salvati et al.	2006/0078618 A1	4/2006	Constantinides et al.
2004/0176336 A1	9/2004	Rodriguez	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0100180 A1	5/2006	Nubbemeyer et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0106004 A1	5/2006	Brody et al.
2004/0191276 A1	9/2004	Muni	2006/0110415 A1	5/2006	Gupta
2004/0198706 A1	10/2004	Carrara	2006/0111424 A1	5/2006	Salvati et al.
2004/0210280 A1	10/2004	Liedtke	2006/0121102 A1	6/2006	Chiang
2004/0213744 A1	10/2004	Lulla et al.	2006/0121626 A1	6/2006	Imrich
2004/0219124 A1	11/2004	Gupta	2006/0134188 A1	6/2006	Podhaisky et al.
2004/0225140 A1	11/2004	Fernandez et al.	2006/0135619 A1	6/2006	Kick et al.
2004/0234606 A1	11/2004	Levine et al.	2006/0165744 A1	7/2006	Jamil et al.
2004/0241219 A1	12/2004	Hille et al.	2006/0193789 A1	8/2006	Tamarkin et al.
2004/0253319 A1	12/2004	Netke et al.	2006/0194775 A1	8/2006	Tofovic et al.
2004/0259817 A1	12/2004	Waldon et al.	2006/0204557 A1	9/2006	Gupta et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0233743 A1	10/2006	Kelly
2005/0003003 A1	1/2005	Basu et al.	2006/0233841 A1	10/2006	Brodbeck et al.
2005/0004088 A1	1/2005	Hesch	2006/0235037 A1	10/2006	Purandare et al.
2005/009800 A1	1/2005	Thumbeck et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0014729 A1	1/2005	Pulaski	2006/0246122 A1	11/2006	Langguth et al.
2005/0020550 A1	1/2005	Morris et al.	2006/0247216 A1	11/2006	Haj-Yehia
2005/0020552 A1	1/2005	Aschkenasay et al.	2006/0247221 A1	11/2006	Coelingh et al.
2005/0021009 A1	1/2005	Massara et al.	2006/0251581 A1	11/2006	McIntyre et al.
2005/0025833 A1	2/2005	Aschkenasay et al.	2006/0252049 A1	11/2006	Shuler et al.
2005/0031651 A1	2/2005	Gervais et al.	2006/0257472 A1	11/2006	Neilsen
2005/0042173 A1	2/2005	Besse et al.	2006/0275218 A1	12/2006	Tamarkin et al.
2005/0042268 A1	2/2005	Aschkenasay et al.	2006/0275360 A1	12/2006	Ahmed et al.
2005/0048116 A1	3/2005	Straub et al.	2006/0276414 A1	12/2006	Coelingh et al.
2005/0054991 A1	3/2005	Tobyn et al.	2006/0280771 A1	12/2006	Groenewegen et al.
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0280797 A1	12/2006	Shoichet et al.
2005/0085453 A1	4/2005	Govindarajan	2006/0280800 A1	12/2006	Nagi et al.
2005/0101579 A1	5/2005	Shippen	2006/0292223 A1	12/2006	Woolfson et al.
2005/0113350 A1	5/2005	Duesterberg et al.	2007/0004693 A1	1/2007	Woolfson et al.
2005/0118244 A1	6/2005	Theobald et al.	2007/0004694 A1	1/2007	Woolfson et al.
2005/0118272 A1	6/2005	Besse et al.	2007/0009559 A1	1/2007	Li et al.
2005/0129756 A1	6/2005	Podhaisky et al.	2007/0009594 A1	1/2007	Grubb et al.
2005/0152956 A1	7/2005	Dudley	2007/0010550 A1	1/2007	McKenzie
2005/0153946 A1	7/2005	Hirsh et al.	2007/0014839 A1	1/2007	Bracht
2005/0164977 A1	7/2005	Coelingh Bennink	2007/0015698 A1	1/2007	Kleinman et al.
2005/0182105 A1	8/2005	Nirschl et al.	2007/0021360 A1	1/2007	Nyce et al.
2005/0186141 A1	8/2005	Gonda et al.	2007/0027201 A1	2/2007	McComas et al.
2005/0187267 A1	8/2005	Hamann et al.	2007/0031491 A1	2/2007	Levine et al.
2005/0192253 A1	9/2005	Salvati et al.	2007/0037780 A1	2/2007	Ebert et al.
2005/0192310 A1	9/2005	Gavai et al.	2007/0037782 A1	2/2007	Hibino et al.
2005/0196434 A1	9/2005	Briere	2007/0042038 A1	2/2007	Besse
2005/0207990 A1	9/2005	Funke et al.	2007/0060589 A1	3/2007	Purandare et al.
2005/0214384 A1	9/2005	Juturu et al.	2007/0066628 A1	3/2007	Zhang et al.
2005/0220825 A1	10/2005	Funke et al.	2007/0066637 A1	3/2007	Zhang et al.
2005/0220900 A1	10/2005	Popp et al.	2007/0066675 A1	3/2007	Zhang et al.
2005/0222106 A1	10/2005	Bracht	2007/0078091 A1	4/2007	Hubles et al.
2005/0239747 A1	10/2005	Yang et al.	2007/0088029 A1	4/2007	Balog et al.
2005/0239758 A1	10/2005	Roby	2007/0093548 A1	4/2007	Diffendal et al.
2005/0244360 A1	11/2005	Billoni	2007/0116729 A1	5/2007	Palepu
2005/0244522 A1	11/2005	Carrara et al.	2007/0116829 A1	5/2007	Prakash et al.
2005/0245902 A1	11/2005	Cornish et al.	2007/0128263 A1	6/2007	Gargiulo et al.
2005/0250746 A1	11/2005	Iammatteo	2007/0154533 A1	7/2007	Dudley
2005/0250750 A1	11/2005	Cummings et al.	2007/0167418 A1	7/2007	Ferguson
2005/0250753 A1	11/2005	Fink et al.	2007/0178166 A1	8/2007	Bernstein et al.
2005/0256028 A1	11/2005	Yun et al.	2007/0184558 A1	8/2007	Roth et al.
2005/0266078 A1	12/2005	Jorda et al.	2007/0185068 A1	8/2007	Ferguson et al.
2005/0266088 A1	12/2005	Hinrichs et al.	2007/0190022 A1	8/2007	Bacopoulos et al.
2005/0271597 A1	12/2005	Keith	2007/0191319 A1	8/2007	Ke et al.
2005/0271598 A1	12/2005	Frieman et al.	2007/0196415 A1	8/2007	Chen et al.
2005/0272685 A1	12/2005	Hung	2007/0196433 A1	8/2007	Ron et al.
2005/0272712 A1	12/2005	Grubb et al.	2007/0207225 A1	9/2007	Squadrito
2006/0009428 A1	1/2006	Grubb et al.	2007/0225281 A1	9/2007	Zhang et al.
2006/0014728 A1	1/2006	Chwalisz et al.	2007/0232574 A1	10/2007	Galey et al.
2006/0018937 A1	1/2006	Friedman et al.	2007/0238713 A1	10/2007	Gast et al.
2006/0019978 A1	1/2006	Balog	2007/0243229 A1	10/2007	Smith et al.
2006/0020002 A1	1/2006	Salvati et al.	2007/0248658 A1	10/2007	Zurdo et al.
2006/0030615 A1	2/2006	Fensome et al.	2007/0254858 A1	11/2007	Cronk
2006/0034889 A1	2/2006	Jo et al.	2007/0255197 A1	11/2007	Humberstone et al.
2006/0034904 A1	2/2006	Weimann	2007/0264309 A1	11/2007	Chollet et al.
2006/0051391 A1	3/2006	Dvoskin et al.	2007/0264345 A1	11/2007	Eros et al.
2006/0052341 A1	3/2006	Cornish et al.	2007/0264349 A1	11/2007	Lee et al.

US 8,987,237 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2007/0286819 A1	12/2007	Devries et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0287688 A1	12/2007	Chan et al.	2009/0181088 A1	7/2009	Song et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0186081 A1	7/2009	Holm et al.
2007/0292359 A1	12/2007	Friedman et al.	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0203658 A1	8/2009	Marx et al.
2007/0292461 A1	12/2007	Tamarkin et al.	2009/0214474 A1	8/2009	Jennings
2007/0292493 A1	12/2007	Briere	2009/0227025 A1	9/2009	Nichols et al.
2007/0298089 A1	12/2007	Saeki et al.	2009/0227550 A1	9/2009	Mattern
2008/0026035 A1	1/2008	Chollet et al.	2009/0232897 A1	9/2009	Sahoo et al.
2008/0026040 A1	1/2008	Farr et al.	2009/0258096 A1	10/2009	Cohen
2008/0026062 A1	1/2008	Farr et al.	2009/0264395 A1	10/2009	Creasy et al.
2008/0038219 A1	2/2008	Mosbaugh et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0038350 A1	2/2008	Gerecke et al.	2009/0285772 A1	11/2009	Phiasivongsa et al.
2008/0039405 A1	2/2008	Langley et al.	2009/0285869 A1	11/2009	Trimble
2008/0050317 A1	2/2008	Tamarkin et al.	2009/0318558 A1	12/2009	Kim et al.
2008/0051351 A1	2/2008	Ghisalberti	2009/0324714 A1	12/2009	Liu et al.
2008/0063607 A1	3/2008	Tamarkin et al.	2009/0325916 A1	12/2009	Zhang et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0069791 A1	3/2008	Beissert	2010/0028360 A1	2/2010	Atwood
2008/0085877 A1	4/2008	Bortz	2010/0034838 A1	2/2010	Staniforth et al.
2008/0095831 A1	4/2008	Mc Graw	2010/0034880 A1	2/2010	Sintov et al.
2008/0095838 A1	4/2008	Abou Chakra-Vernet	2010/0040671 A1	2/2010	Ahmed et al.
2008/0113953 A1	5/2008	Devries et al.	2010/0048523 A1	2/2010	Bachman et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0055138 A1	3/2010	Margulies et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0074959 A1	3/2010	Hansom et al.
2008/0125402 A1	5/2008	Diliberti et al.	2010/0086501 A1	4/2010	Chang et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0086599 A1	4/2010	Huemel et al.
2008/0138390 A1	6/2008	Hsu et al.	2010/0105071 A1	4/2010	Lerner et al.
2008/0139392 A1	6/2008	Acosta-Zara et al.	2010/0119585 A1	5/2010	Laufer et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0129320 A1	5/2010	Phiasivongsa et al.
2008/0153789 A1	6/2008	Dmowski et al.	2010/0136105 A1	6/2010	Chen et al.
2008/0175814 A1	7/2008	Phiasivongsa et al.	2010/0137265 A1	6/2010	Leonard
2008/0175905 A1	7/2008	Liu et al.	2010/0137271 A1	6/2010	Chen et al.
2008/0175908 A1	7/2008	Liu et al.	2010/0143420 A1	6/2010	Shenoy et al.
2008/0188829 A1	8/2008	Creasy	2010/0143481 A1	6/2010	Shenoy et al.
2008/0206156 A1	8/2008	Cronk	2010/0150993 A1	6/2010	Theobald et al.
2008/0206159 A1	8/2008	Tamarkin et al.	2010/0152144 A1	6/2010	Hermsmeyer
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0168228 A1	7/2010	Bose et al.
2008/0214512 A1	9/2008	Seitz et al.	2010/0183723 A1	7/2010	Laurent-Applegate
2008/0220069 A1	9/2008	Allison	2010/0184736 A1	7/2010	Coelingh Bennink et al.
2008/0226698 A1	9/2008	Tang et al.	2010/0190758 A1	7/2010	Fauser et al.
2008/0227763 A1	9/2008	Lanquettein et al.	2010/0204326 A1	8/2010	D Souza
2008/0234199 A1	9/2008	Katamreddym et al.	2010/0210994 A1	8/2010	Zarif
2008/0234240 A1	9/2008	Duesterberg et al.	2010/0221195 A1	9/2010	Tamarkin et al.
2008/0255078 A1	10/2008	Katamreddym et al.	2010/0227797 A1	9/2010	Axelson et al.
2008/0255089 A1	10/2008	Katamreddym et al.	2010/0240626 A1	9/2010	Kulkarni et al.
2008/0261931 A1	10/2008	Hedner et al.	2010/0247482 A1	9/2010	Cui et al.
2008/0299220 A1	12/2008	Tamarkin et al.	2010/0247632 A1	9/2010	Dong et al.
2008/0306036 A1	12/2008	Katamreddym et al.	2010/0247635 A1	9/2010	Rosenberg et al.
2008/0312197 A1	12/2008	Rodriguez	2010/0255085 A1	10/2010	Liu et al.
2008/0312198 A1	12/2008	Rodriguez	2010/0273730 A1	10/2010	Hsu et al.
2008/0319078 A1	12/2008	Katamreddym et al.	2010/0278759 A1	11/2010	Murad
2009/0004246 A1	1/2009	Woolfson et al.	2010/0279988 A1	11/2010	Setiawan et al.
2009/0010968 A1	1/2009	Allart et al.	2010/0291191 A1	11/2010	Shoichet et al.
2009/0011041 A1	1/2009	Musaeva et al.	2010/0292199 A1	11/2010	Leverd et al.
2009/0017120 A1	1/2009	Trimble et al.	2010/0303825 A9	12/2010	Sirbasku
2009/0022683 A1	1/2009	Song et al.	2010/0312137 A1	12/2010	Gilmour et al.
2009/0047357 A1	2/2009	Tomohira et al.	2010/0316724 A1	12/2010	Whitfield et al.
2009/0053294 A1	2/2009	Prendergast	2010/0322884 A1	12/2010	Dipietro et al.
2009/0060982 A1	3/2009	Rox et al.	2010/0330168 A1	12/2010	Gicquel et al.
2009/0060997 A1	3/2009	Seitz et al.	2011/0028439 A1	2/2011	Witt-Enderby et al.
2009/0068118 A1	3/2009	Eini et al.	2011/0039814 A1	2/2011	Huatan et al.
2009/0081206 A1	3/2009	Leibovitz	2011/0053845 A1	3/2011	Levine et al.
2009/0081278 A1	3/2009	De Graaff et al.	2011/0076775 A1	3/2011	Stewart et al.
2009/0081303 A1	3/2009	Savoir et al.	2011/0076776 A1	3/2011	Stewart et al.
2009/0092656 A1	4/2009	Klamerus et al.	2011/0086825 A1	4/2011	Chatroux
2009/0093440 A1	4/2009	Murad	2011/0087192 A1	4/2011	Uhland et al.
2009/0098069 A1	4/2009	Vacca	2011/0091555 A1	4/2011	De Luigi Bruschi et al.
2009/0099106 A1	4/2009	Phiasivongsa et al.	2011/0098258 A1	4/2011	Masini-Eteve et al.
2009/0099149 A1	4/2009	Liu et al.	2011/0098631 A1	4/2011	McIntyre et al.
2009/0130029 A1	5/2009	Tamarkin et al.	2011/0104268 A1	5/2011	Pachot et al.
2009/0131385 A1	5/2009	Voskuhl	2011/0104289 A1	5/2011	Savoir Vilboeuf et al.
2009/0137478 A1	5/2009	Bernstein et al.	2011/0130372 A1	6/2011	Agostinacchio et al.
2009/0137538 A1	5/2009	Klamerus et al.	2011/0135719 A1	6/2011	Besins et al.
2009/0143344 A1	6/2009	Chang	2011/0142945 A1	6/2011	Chen et al.
			2011/0152840 A1	6/2011	Lee et al.
			2011/0158920 A1	6/2011	Morley et al.
			2011/0171140 A1	7/2011	Illum et al.

US 8,987,237 B2

Page 8

(56)

References Cited**U.S. PATENT DOCUMENTS**

2011/0182997 A1	7/2011	Lewis et al.	2012/0316496 A1	12/2012	Hoffmann et al.
2011/0190201 A1	8/2011	Hyde et al.	2012/0321579 A1	12/2012	Edelson et al.
2011/0195031 A1	8/2011	Du	2012/0322779 A9	12/2012	Voskuhl
2011/0195114 A1	8/2011	Carrara et al.	2012/0328549 A1	12/2012	Edelson et al.
2011/0195944 A1	8/2011	Mura et al.	2012/0329738 A1	12/2012	Liu
2011/0217341 A1	9/2011	Sah	2013/0004619 A1	1/2013	Chow et al.
2011/0238003 A1	9/2011	Bruno-Raimondi et al.	2013/0011342 A1	1/2013	Tamarkin et al.
2011/0244043 A1	10/2011	Xu et al.	2013/0017239 A1	1/2013	Viladot et al.
2011/0250256 A1	10/2011	Hyun-Oh et al.	2013/0022674 A1	1/2013	Dudley et al.
2011/0250259 A1	10/2011	Buckman	2013/0023505 A1	1/2013	Garfield et al.
2011/0250274 A1	10/2011	Shaked et al.	2013/0023823 A1	1/2013	Simpson et al.
2011/0256092 A1	10/2011	Phiasivongsa et al.	2013/0028850 A1	1/2013	Tamarkin et al.
2011/0262373 A1	10/2011	Umbert	2013/0029947 A1	1/2013	Nachaegari et al.
2011/0262494 A1	10/2011	Achleitner et al.	2013/0029957 A1	1/2013	Giliyar et al.
2011/0268665 A1	11/2011	Tamarkin et al.	2013/0045266 A1	2/2013	Choi et al.
2011/0275584 A1	11/2011	Wilckens et al.	2013/0045953 A1	2/2013	Sitruck-Ware et al.
2011/0281832 A1	11/2011	Li et al.	2013/0059795 A1	3/2013	Lo et al.
2011/0287094 A1	11/2011	Penhasi et al.	2013/0064897 A1	3/2013	Binay
2011/0293720 A1	12/2011	General et al.	2013/0072466 A1	3/2013	Choi et al.
2011/0294738 A1	12/2011	Ren et al.	2013/0084257 A1	4/2013	Ishida et al.
2011/0300167 A1	12/2011	McMurry et al.	2013/0085123 A1	4/2013	Li et al.
2011/0301087 A1	12/2011	McBride et al.	2013/0089574 A1	4/2013	Schmidt-Gollwitzer et al.
2011/0306579 A1	12/2011	Stein	2013/0090318 A1	4/2013	Ulmann et al.
2011/0311592 A1	12/2011	Birbara	2013/0102781 A1	4/2013	Bevill et al.
2011/0312927 A1	12/2011	Nachaegari et al.	2013/0108551 A1	5/2013	Langereis et al.
2011/0312928 A1	12/2011	Nachaegari et al.	2013/0116215 A1	5/2013	Coma et al.
2011/0318405 A1	12/2011	Erwin	2013/0116222 A1	5/2013	Arnold et al.
2011/0318431 A1	12/2011	Gulati	2013/0122051 A1	5/2013	Abidi et al.
2012/0009276 A1	1/2012	De Groot	2013/0123175 A1	5/2013	Hill et al.
2012/0015350 A1	1/2012	Nabatiyan et al.	2013/0123220 A1	5/2013	Queiroz
2012/0021041 A1	1/2012	Rossi et al.	2013/0123351 A1	5/2013	Dewitt
2012/0028888 A1	2/2012	Janz et al.	2013/0129818 A1	5/2013	Bernick et al.
2012/0028910 A1	2/2012	Combal et al.	2013/0131027 A1	5/2013	Pakkalin et al.
2012/0028936 A1	2/2012	Gloger et al.	2013/0131028 A1	5/2013	Snyder et al.
2012/0045532 A1	2/2012	Cohen	2013/0131029 A1	5/2013	Bakker et al.
2012/0046264 A1	2/2012	Simes et al.	2013/0149314 A1	6/2013	Bullerdiek et al.
2012/0046518 A1	2/2012	Yoakum et al.	2013/0164225 A1	6/2013	Tamarkin et al.
2012/0052077 A1	3/2012	Truitt et al.	2013/0164346 A1	6/2013	Lee et al.
2012/0058171 A1	3/2012	De Graaff et al.	2013/0165744 A1	6/2013	Carson et al.
2012/0058962 A1	3/2012	Cumming et al.	2013/0178452 A1	7/2013	King
2012/0058979 A1	3/2012	Keith et al.	2013/0183254 A1	7/2013	Zhou
2012/0064135 A1	3/2012	Levin et al.	2013/0183325 A1	7/2013	Bottoni et al.
2012/0065179 A1	3/2012	Andersson	2013/0189193 A1	7/2013	Tamarkin et al.
2012/0087872 A1	4/2012	Tamarkin et al.	2013/0189196 A1	7/2013	Tamarkin et al.
2012/0101073 A1	4/2012	Mannion et al.	2013/0189230 A1	7/2013	Shoichet et al.
2012/0121517 A1	5/2012	Song et al.	2013/0189368 A1	7/2013	Mosqueira et al.
2012/0121692 A1	5/2012	Xu et al.	2013/0210709 A1	8/2013	McMurry et al.
2012/0122829 A1	5/2012	Taravella et al.	2013/0216550 A1	8/2013	Penninger et al.
2012/0128625 A1	5/2012	Shalwitz et al.	2013/0216596 A1	8/2013	Viladot Petit et al.
2012/0128654 A1	5/2012	Terpstra et al.	2013/0224177 A1	8/2013	Kim et al.
2012/0128683 A1	5/2012	Shantha	2013/0224257 A1	8/2013	Sah et al.
2012/0128733 A1	5/2012	Perrin et al.	2013/0224268 A1	8/2013	Alam et al.
2012/0128777 A1	5/2012	Keck et al.	2013/0224300 A1	8/2013	Maggio
2012/0129773 A1	5/2012	Geier et al.	2013/0225412 A1	8/2013	Sardari Lodriche et al.
2012/0129819 A1	5/2012	Vancaillie et al.	2013/0225542 A1	8/2013	Poegh et al.
2012/0136013 A1	5/2012	Li et al.	2013/0226113 A1	8/2013	Schumacher et al.
2012/0142645 A1	6/2012	Marx	2013/0243696 A1	9/2013	Wang et al.
2012/0148670 A1	6/2012	Kim et al.	2013/0245253 A1	9/2013	Marx et al.
2012/0149748 A1	6/2012	Shanler et al.	2013/0245570 A1	9/2013	Jackson
2012/0172343 A1	7/2012	Lindenthal et al.	2013/0261096 A1	10/2013	Merian et al.
2012/0184515 A1	7/2012	Klar et al.	2013/0266645 A1	10/2013	Becker et al.
2012/0231052 A1	9/2012	Sitruck-Ware et al.	2013/0267485 A1	10/2013	Da Silva Maia Filho
2012/0232011 A1	9/2012	Kneissel et al.	2013/0273167 A1	10/2013	Lee et al.
2012/0232042 A1	9/2012	Klar et al.	2013/0274211 A1	10/2013	Burman et al.
2012/0263679 A1	10/2012	Marlow et al.	2013/0280213 A1	10/2013	Voskuhl
2012/0269721 A1	10/2012	Weng et al.	2013/0316374 A1	11/2013	Penninger et al.
2012/0269878 A2	10/2012	Cantor et al.	2013/0317065 A1	11/2013	Tatani et al.
2012/0277249 A1	11/2012	Andersson et al.	2013/0317315 A1	11/2013	Lu et al.
2012/0277727 A1	11/2012	Doshi et al.	2013/0324565 A1	12/2013	Li et al.
2012/0283671 A1	11/2012	Shibata et al.	2013/0331363 A1	12/2013	Li et al.
2012/0295911 A1	11/2012	Mannion et al.	2013/0338124 A1	12/2013	Li et al.
2012/0301517 A1	11/2012	Zhang et al.	2013/0345187 A1	12/2013	Rodriguez Oquendo
2012/0301538 A1	11/2012	Gordon-Beresford et al.	2014/0018335 A1	1/2014	Tatani et al.
2012/0302535 A1	11/2012	Caufriez et al.	2014/0024590 A1	1/2014	Weidhaas et al.
2012/0316130 A1	12/2012	Hendrix	2014/0031289 A1	1/2014	Song et al.
			2014/0031323 A1	1/2014	Perez
			2014/0066416 A1	3/2014	Leunis et al.
			2014/0072531 A1	3/2014	Kim et al.
			2014/0079686 A1	3/2014	Barman et al.

US 8,987,237 B2

Page 9

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2014/0088058 A1	3/2014	Maurizio	WO	03077923 A1	9/2003	
2014/0088059 A1	3/2014	Perumal et al.	WO	03082254 A1	10/2003	
2014/0094426 A1	4/2014	Drummond et al.	WO	03092588 A2	11/2003	
2014/0100159 A1	4/2014	Conrad	WO	WO2004014432	2/2004	
2014/0100206 A1	4/2014	Bernick et al.	WO	2004017983 A1	3/2004	
2014/0113889 A1	4/2014	Connor et al.	WO	2004032897 A2	4/2004	
2014/0127185 A1	5/2014	Stein et al.	WO	2004052336 A2	6/2004	
2014/0127280 A1	5/2014	Duesterberg et al.	WO	2004054540 A2	7/2004	
2014/0127308 A1	5/2014	Opara et al.	WO	2004080413 A2	9/2004	
2014/0128798 A1	5/2014	Janson et al.	WO	2005027911 A1	3/2005	
2014/0186332 A1	7/2014	Ezrin et al.	WO	2005030175 A1	4/2005	
2014/0187487 A1	7/2014	Shoichet et al.	WO	2005087194 A1	9/2005	
2014/0193523 A1	7/2014	Henry	WO	2005087199 A2	9/2005	
2014/0194396 A1	7/2014	Li et al.	WO	WO2005081825	9/2005	
2014/0206616 A1	7/2014	Ko et al.	WO	2005105059 A1	11/2005	
FOREIGN PATENT DOCUMENTS						
EP 0275716 A1	7/1988		WO	2005115335 A1	12/2005	
EP 0622075 A1	11/1994		WO	2005120470 A1	12/2005	
EP 0785211 A1	1/1996		WO	2007045027 A1	4/2007	
EP 0811381 A1	6/1997		WO	2007103294 A2	9/2007	
EP 0785212 A1	7/1997		WO	WO2007120868	10/2007	
EP 1094781 B1	7/2008		WO	2007123790 A1	11/2007	
EP 2191833 A1	6/2010		WO	2007124250 A2	11/2007	
GB 1589946 A1	2/1921		WO	2007144151 A1	12/2007	
GB 452238 A	8/1936		WO	2008049516 A3	5/2008	
GB 720561 A	12/1954		WO	2008152444 A2	12/2008	
GB 848881 A	9/1960		WO	2009002542 A1	12/2008	
GB 874368 A	8/1961		WO	2009036311 A1	3/2009	
IN 216026 A	3/2008		WO	2009040818	4/2009	
IN 2005KO00053 A	9/2009		WO	2009069006 A2	6/2009	
IN 244217 A	11/2010		WO	2009098072 A2	8/2009	
WO 9011064 A1	10/1990		WO	2009133352 A2	11/2009	
WO 9317686 A1	9/1993		WO	2010033188 A2	3/2010	
WO 9422426 A1	10/1994		WO	WO2010146872	12/2010	
WO 9530409 A1	11/1995		WO	2011000210 A1	1/2011	
WO 9609826 A2	4/1996		WO	2011073995 A2	6/2011	
WO WO9619975	7/1996		WO	2011120084 A1	10/2011	
WO 9630000 A1	10/1996		WO	2011128336 A1	10/2011	
WO 9705491	2/1997		WO	2012009778 A2	1/2012	
WO 9743989 A1	11/1997		WO	2012024361 A1	2/2012	
WO 9810293 A1	3/1998		WO	WO2012055814 A1	5/2012	
WO 9832465 A1	7/1998		WO	WO2012055840 A1	5/2012	
WO 9851280 A1	11/1998		WO	WO2012065740	5/2012	
WO 9932072	7/1999		WO	WO2012098090 A1	7/2012	
WO 9939700 A1	8/1999		WO	WO2012116277 A1	8/2012	
WO 9942109 A1	8/1999		WO	WO2012118563 A2	9/2012	
WO 9943304	9/1999		WO	WO2012120365 A1	9/2012	
WO 9948477 A1	9/1999		WO	WO2012127501 A2	9/2012	
WO 9953910 A2	10/1999		WO	WO2012156561 A1	11/2012	
WO 9963974 A2	12/1999		WO	WO2012156822 A1	11/2012	
WO 0001351 A1	1/2000		WO	WO2012158483 A2	11/2012	
WO 0006175 A1	2/2000		WO	WO2012166909 A1	12/2012	
WO 0038659 A1	7/2000		WO	WO2012170578 A1	12/2012	
WO 0045795 A2	8/2000		WO	WO2013011501 A1	1/2013	
WO 0050007 A1	8/2000		WO	WO2013025449 A1	2/2013	
WO 0059577 A1	10/2000		WO	WO2013028639 A1	2/2013	
WO 0076522 A1	12/2000		WO	WO2013035101 A1	3/2013	
WO 0137808 A1	5/2001		WO	WO2013044067 A1	3/2013	
WO 0154699 A1	8/2001		WO	WO2013045404 A2	4/2013	
WO 0160325 A1	8/2001		WO	WO2013059285 A1	4/2013	
WO 0207700 A2	2/2002		WO	WO2013063279 A1	5/2013	
WO 0211768 A1	2/2002		WO	WO2013064620 A1	5/2013	
WO 0222132 A2	3/2002		WO	WO2013071281 A1	5/2013	
WO 0240008 A2	5/2002		WO	WO2013088254	6/2013	
WO WO0241878	5/2002		WO	WO2013102665 A1	7/2013	
WO 02053131 A1	7/2002		WO	WO2013106437 A1	7/2013	
WO 02078602 A2	10/2002		WO	WO2013113690	8/2013	
WO 02078604 A2	10/2002		WO	WO2013124415 A1	8/2013	
WO WO03028667	4/2003		WO	WO2013127727 A1	9/2013	
WO 03041718 A1	5/2003		WO	WO2013127728 A1	9/2013	
WO 03041741 A1	5/2003		WO	WO2013144356 A1	10/2013	
WO 03068186 A1	8/2003					

US 8,987,237 B2

Page 10

(56)

References Cited**FOREIGN PATENT DOCUMENTS**

WO WO2013149258 A2 10/2013
 WO WO2013158454 A2 10/2013
 WO WO2013170052 A1 11/2013
 WO 2013192248 A1 12/2013
 WO 2013192249 A1 12/2013
 WO 2013192250 A1 12/2013
 WO 2013192251 A1 12/2013
 WO WO2013178587 A1 12/2013
 WO WO2013181449 A1 12/2013
 WO WO2014001904 A1 1/2014
 WO WO2014004424 A1 1/2014
 WO WO2014009434 A1 1/2014
 WO WO2014018569 A1 1/2014
 WO WO2014018570 A1 1/2014
 WO WO2014018571 A2 1/2014
 WO WO2014018856 A1 1/2014
 WO WO2014018932 A2 1/2014
 WO WO2014031958 A1 2/2014
 WO WO2014041120 A1 3/2014
 WO WO2014052792 A1 4/2014
 WO WO2014056897 A1 4/2014
 WO WO2014066442 A2 5/2014
 WO WO2014074846 A1 5/2014
 WO WO2014076231 A1 5/2014
 WO WO2014076569 A2 5/2014
 WO WO2014081598 A1 5/2014
 WO WO2014086739 A1 6/2014
 WO WO2014093114 A1 6/2014
 WO WO2014104784 A1 7/2014

OTHER PUBLICATIONS

USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.
 USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.
 Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.
 Azem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.
 Azure Pharma, Inc., "ELESTRINTM—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages (Aug. 2009).
 Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ERA and ERb", Endocrinology, 149(10): 4857-4870 (Oct. 2008).
 Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).
 Tahition Noni, "Body Balance Cream," http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/, (undated), 1 page.
 Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.
 Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).
 Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).
 Diramio, "Polyethylene Glycol Methacrylate/Dimethylacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia—Masters of Science Thesis, 131 pages (2004). http://athenaenum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1.
 Du, et al. "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 11, (Feb. 2013).
 Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.
 Fuchs, et al., "The Effects of on Estrogen and Glycolic Acid Cream on the Focal Skin of Postmenopausal Women: A Randomized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.
 Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.
 Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.
 Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).
 Kincl, et al., "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.
 Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.
 Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Periestrual and Postinsemination Periods in Dairy Cattle," Biol Reprod. 35(2):300-311 (1986). Abstract Only.
 Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.
 NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.
 Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, min.sagepub.com. Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
 Panchagnula et al., "Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," J Pharm Pharmacol. 43(9):609-614 (Sep. 1991). Abstract Only.
 Patel, et al., "Transdermal Drug Delivery System: A Review," www.thepharmajournal.com, vol. 1 No. 4 2012.
 Salole, "The physicochemical properties of oestradiol," Journal of Pharmaceutical & Biomedical Analysis, 5(7):635-648 (1987).
 Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," American Journal of Public Health, Published online ahead of print Jul. 18, 2013.
 Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014.
 Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," The American College of Obstetricians and Gynecologists, vol. 112, No. 5, Nov. 2008.
 Sitruk-Ware, et al., "Oral Micronized Progesterone," Department of Reproductive Endocrinology, vol. 36, No. 4, pp. 373-402, Oct. 1987.
 Sitruk-Ware, et al., "Progesterogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," Menopause: The Journal of the North American Menopause Society, vol. 9, No. 1, pp. 6-15, 2002.
 Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," JAMA Internal Medicine <http://archinte.jamanetwork.com>, Sep. 30, 2013.
 Stanczyk, et al. "Ethinyl Estradiol and 17 β -Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment," Departments of Obstetrics and Gynecology and

US 8,987,237 B2

Page 11

(56)

References Cited

OTHER PUBLICATIONS

- Preventive Medicine, University of Southern California Keck School of Medicine, Contraception 87 706-727, (2013).
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," Pharmaceutical Research, 21(2):201-230 (Feb. 2004).
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," Skin Pharmacol Physiol, 19:106-121 (2006). http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf.
- Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," The British Medical Journal, vol. 280, No. 6217, Mar. 22, 1980.
- Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," Springer Science+Business Media B.V., Breast Cancer Res Treat 101:125-134, (2007).
- USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- US 6,214,374, 04/2001, Schmirler et al. (withdrawn).
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of *Thevetia peruviana* and *Hura crepitans* Seed oils using GC-FID, Fountain Journal of Nat. and Appl. Sciences, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, Sci. Agric., vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, Clean Techn Environ Policy, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, Obstetrics & Gynecology, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Suplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saftey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate—Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, Cereal Chem., vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helveticae, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PhamSciTech, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T, et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. SteroidBiochem. Mol. Biol. (2013), Elsevier.
- Wiranichapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, pp. 1110-1111, CRC PRESS, Boca Raton, London, New York, Wash. D.C.
- Yue, W, Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier.

US 8,987,237 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- Kuhnert-Brandstatter, M., Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas*, The European Menopaus Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffey, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol.Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*,35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, *Intn'l Union of Crystallography*, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Phasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/_Progynova%20TS%20100%2012%20Patches__Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem.Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, Natioinoal Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, *Obstetrics & Gynecology*.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation(PIHn), *Scanning* vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, *SciFinder*, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.

US 8,987,237 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Cendejas-Santana, G., et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A., et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O., et al., Crystal data on progesterone (C₂₁H₃₀O₂), desoxycorticosterone (C₂₁H₃₀O₃), corticosterone (C₂₁H₃₀O₄) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R., et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helveticae, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, Pharmaceutical Research, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, Journal of General Internal Medicine, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochimica Acta, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S., et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminski, R., et al., EPR Study of the Stable Radical in a γ-Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.
- Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.

US 8,987,237 B2

Page 14

(56)

References Cited

OTHER PUBLICATIONS

- Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.

Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.

ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.

* cited by examiner

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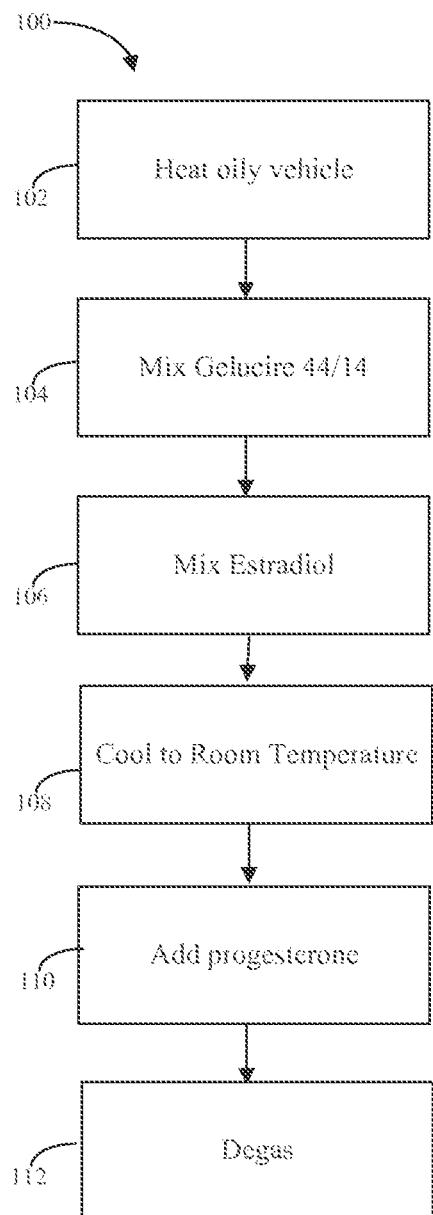
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Fig. 1

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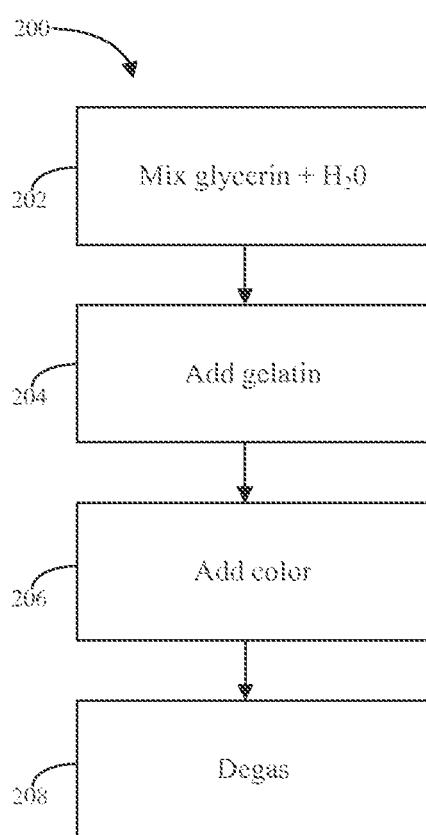


Fig. 2

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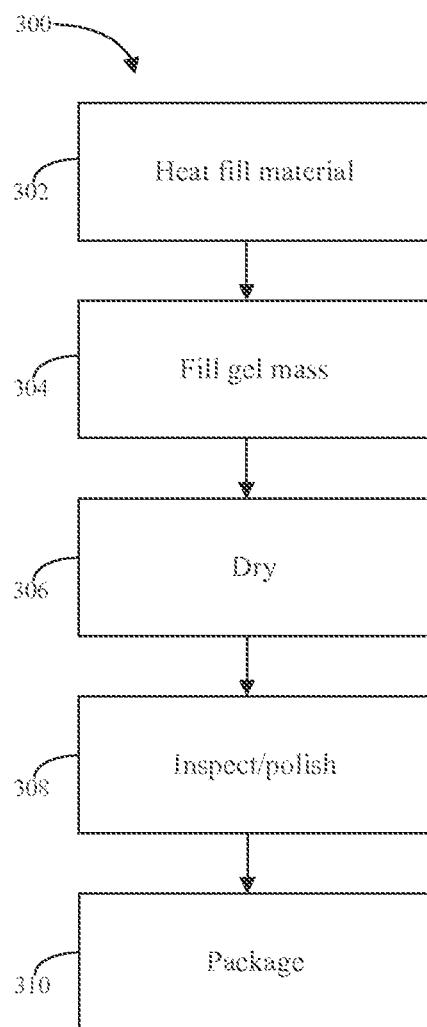


Fig. 3

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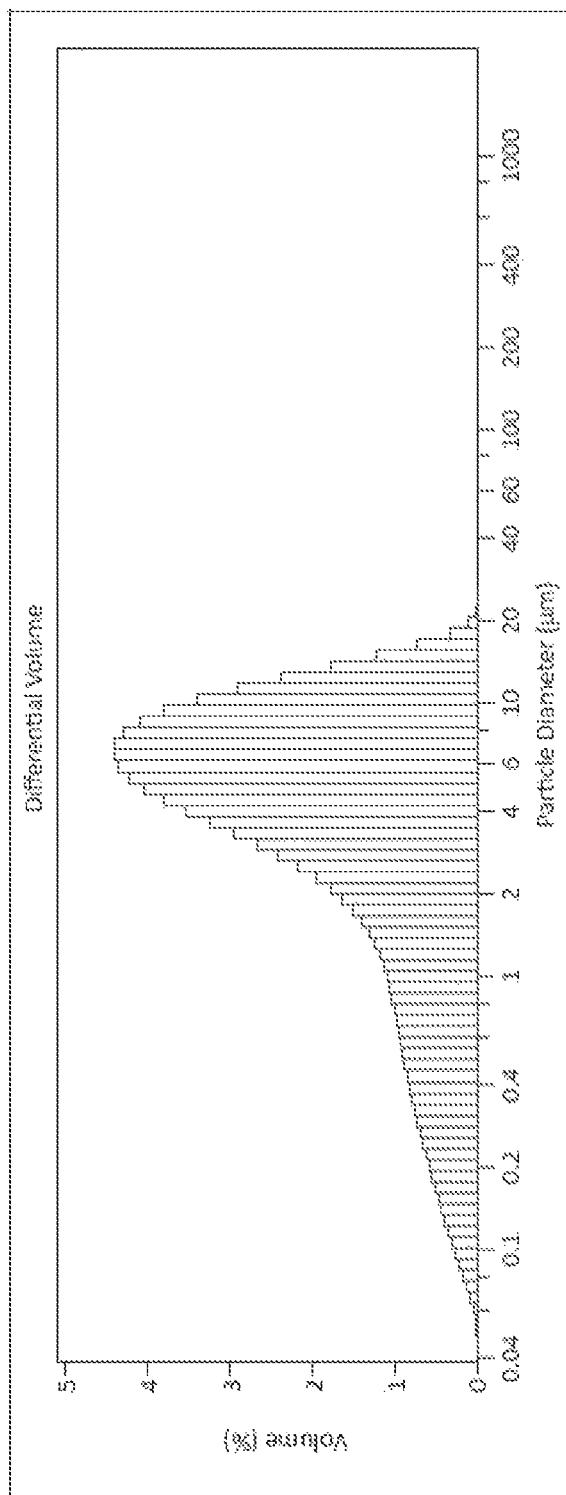


FIG. 4

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1

**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a non-provisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563, 408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

2

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREMPRO (conjugated estrogens/methoxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus methoxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic methoxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

**BRIEF DESCRIPTION OF THE
DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

**DETAILED DESCRIPTION OF THE
ILLUSTRATED EMBODIMENTS**

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

DEFINITIONS

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/

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sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm . The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These

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formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

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Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may

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comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from errone-

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ous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

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EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

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TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

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Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM(Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

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TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM(Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether)MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	Amount/ % w/w	Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	322.97	99.38	3.23 kg
Total	100	3.25 kg	

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

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Example 7

Progesterone Solubility

- 5 In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 10 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.
- 15 As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some 20 aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 35 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/ Capric Triglyceride)	27.8

55 In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

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TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides) GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF	82.57	577.97	70.00
TOTAL	100.00	700.00	

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/-2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides)

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mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	200.00	30.77	Active
Lecithin Liquid	qs	qs	Carrier
Butylated Hydroxytoluene (also referred to as "BHT")	1.63	0.25	Lubricant/Emulsifier
	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w (mg)	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2%

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w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median

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particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	Qty/Capsule (mg)	Amount/Batch (kg)	
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF	82.57	577.97	5.78	
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF	10.0	70.00	0.70	
	Total:	100.00	700.00	7.00	

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF	73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF)	1.500	3.00	30.00

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TABLE 16-continued

Item No.	Ingredient(s)	Label Claim (mg)	Qty/ Capsule % w/w (mg)	Amount/ Batch (g)
	Lauroyl polyoxylglycerides (USA FDA IIG), NF			
Total:		100.000	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	Qty/ Capsule % w/w (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33 200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35 2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32 391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00 6.0	60.0
Total:		100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bioavailability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

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The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by 10 dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout 25 the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects 30 were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout 35 the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes 40 prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth 45 check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in 55 one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing 60 blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

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At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of $-70^{\circ}\text{C.}\pm20^{\circ}\text{C.}$ in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to $40^{\circ}\text{C.}\pm5^{\circ}\text{C.}$ Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Heating may be performed until the temperature reaches $80^{\circ}\text{C.}\pm5^{\circ}\text{C.}$

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 208 comprises degassing. The

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resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to $30^{\circ}\text{C.}\pm3^{\circ}\text{C.}$ Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C.}\pm10^{\circ}\text{C.}$ The wedge temperature may be $38^{\circ}\text{C.}\pm3^{\circ}\text{C.}$ The drum cooling temperature may be $4^{\circ}\text{C.}\pm2^{\circ}\text{C.}$ The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm}\pm0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm5\%$ (i.e., $650\pm33\text{ mg}$ and $325\pm16.3\text{ mg}$).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^{\circ}\text{C.}\pm10^{\circ}\text{C.}$ The wedge temperature may be $38^{\circ}\text{C.}\pm3^{\circ}\text{C.}$ The drum cooling temperature may be $4^{\circ}\text{C.}\pm2^{\circ}\text{C.}$ The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm}\pm0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm5\%$ (i.e., $650\pm33\text{ mg}$ and $325\pm16.3\text{ mg}$).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical composition comprising:
a solubilizing agent comprising:
mono- and diglycerides of capric and caprylic acid; and
at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxy-glycerides;
estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;
wherein the estradiol and the progesterone are present in the solubilizing agent, and the estradiol and suspended progesterone are uniformly dispersed.
2. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

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3. The pharmaceutical composition of claim **2**, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, and about 200:1.

4. The pharmaceutical composition of claim **1**, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

5 **5** 5. The pharmaceutical composition of claim **1**, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

6. The pharmaceutical composition of claim **1**, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

7. The pharmaceutical composition of claim **1**, wherein the estradiol is at least 90% solubilized in the solubilizing agent.

8. A pharmaceutical composition comprising:
a solubilizing agent comprising:
monoglycerides and diglycerides of caprylic and capric acid; and
a polyethylene glycol glyceride;
progesterone; and
estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;
wherein the estradiol and the progesterone are present in the solubilizing agent, and the estradiol and progesterone are uniformly dispersed.

9. The pharmaceutical composition of claim **8**, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

10. The pharmaceutical composition of claim **9**, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1 and about 200:1.

11. The pharmaceutical composition of claim **8**, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

12. The pharmaceutical composition of claim **8**, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

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13. The pharmaceutical composition of claim **8**, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

14. The pharmaceutical composition of claim **8**, wherein the estradiol is at least 90% solubilized in the solubilizing agent.

15. A pharmaceutical composition comprising:
a solubilizing agent comprising:
mono- and diglycerides of capric and caprylic acid; and
at least one of lauroyl macrogol-32 glycerides, lauroyl polyoxy-32 glycerides, and lauroyl polyoxylglycerides;
progesterone; and
estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;
wherein the estradiol and the suspended progesterone are present in the solubilizing agent, and the estradiol and suspended progesterone are uniformly dispersed.

16. The pharmaceutical composition of claim **15**, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

17. The pharmaceutical composition of claim **15**, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1 and about 200:1.

18. The pharmaceutical composition of claim **15**, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

19. The pharmaceutical composition of claim **15**, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

20. The pharmaceutical composition of claim **15**, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,987,237 B2
APPLICATION NO. : 14/099562
DATED : March 24, 2015
INVENTOR(S) : Brian A. Bernick et al.

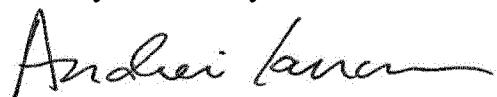
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,987,237 B2
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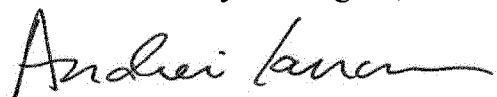
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 24, Claim 15, Line 21: Insert --dispersed-- after “uniformly”.

Signed and Sealed this
Twentieth Day of August, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT E



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(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 8,993,548 B2
(45) **Date of Patent:** *Mar. 31, 2015

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Neda Irani**, Palm Beach Garden, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 14/475,814

(22) Filed: Sep. 3, 2014

(65) **Prior Publication Data**

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Related U.S. Application Data

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(60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

(51) **Int. Cl.**

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A61K 31/57 (2006.01)
A61K 9/16 (2006.01)
A61K 31/565 (2006.01)
A61K 9/70 (2006.01)

(52) **U.S. Cl.**

CPC . *A61K 31/57* (2013.01); *A61K 9/16* (2013.01);
A61K 31/565 (2013.01); *A61K 9/4858* (2013.01); *A61K 9/7023* (2013.01)

USPC 514/169; 424/452

(58) **Field of Classification Search**

CPC A61K 31/57; A61K 31/565
USPC 514/169; 424/452

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,232,438 A	2/1941	Butenandt
4,900,734 A *	2/1990	Maxson et al. 514/171
5,538,736 A	7/1996	Hoffmann et al.
5,556,635 A	9/1996	Istin et al.
5,580,572 A	12/1996	Mikler et al.
5,605,702 A	2/1997	Teillaud et al.
5,607,691 A	3/1997	Hale et al.
5,607,693 A	3/1997	Bonte et al.
5,609,617 A	3/1997	Shealy et al.
5,626,866 A	5/1997	Ebert et al.
5,653,983 A	8/1997	Meybeck et al.
5,660,839 A	8/1997	Allec et al.
5,662,927 A	9/1997	Ehrlich et al.
5,663,160 A	9/1997	Meybeck et al.
5,686,097 A	11/1997	Taskovich et al.
5,693,335 A	12/1997	Xia et al.
5,700,480 A	12/1997	Hille et al.
5,719,197 A	2/1998	Kanios et al.
5,770,220 A	6/1998	Meconi et al.
5,770,227 A	6/1998	Dong et al.
5,780,044 A	7/1998	Yewey et al.
5,780,050 A	7/1998	Jain et al.
5,788,984 A	8/1998	Guenther et al.
5,820,878 A	10/1998	Hirano et al.
5,840,327 A	11/1998	Gale et al.
5,843,468 A	12/1998	Burkoth et al.
5,843,979 A	12/1998	Wille et al.
5,858,394 A	1/1999	Lipp et al.
5,863,552 A	1/1999	Yue

(Continued)

FOREIGN PATENT DOCUMENTS

WO	WO9619975	7/1996
WO	WO241878	5/2002

(Continued)

OTHER PUBLICATIONS

Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.
Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
Gattefossé Sas, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
Gattefossé Sas, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
Gattefossé Sas, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.

(Continued)

Primary Examiner — Dennis J Parad

(74) Attorney, Agent, or Firm — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

US 8,993,548 B2

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(56)

References Cited**U.S. PATENT DOCUMENTS**

5,882,676 A	3/1999	Lee et al.	7,094,228 B2	8/2006	Zhang et al.
5,885,612 A	3/1999	Meconi et al.	7,097,853 B1	8/2006	Garbe et al.
5,888,533 A	3/1999	Dunn	7,105,573 B2	9/2006	Krajcik et al.
5,891,462 A	4/1999	Carrara	7,153,522 B1	12/2006	Ikeura et al.
5,902,603 A	5/1999	Chen et al.	7,175,850 B2	2/2007	Cevc
5,904,931 A	5/1999	Lipp et al.	7,198,800 B1	4/2007	Ko
5,906,830 A	5/1999	Farinas et al.	7,381,427 B2	6/2008	Ancira et al.
5,912,010 A	6/1999	Wille et al.	7,456,159 B2	11/2008	Houze et al.
5,919,477 A	7/1999	Bevan et al.	7,498,303 B2	3/2009	Arnold et al.
5,942,243 A	8/1999	Shah	7,534,780 B2	5/2009	Wyrwa et al.
5,952,000 A	9/1999	Venkateshwaran et al.	7,569,274 B2	8/2009	Besse et al.
5,968,919 A	10/1999	Samour et al.	7,799,769 B2	9/2010	White et al.
5,985,311 A	11/1999	Cordes et al.	7,815,936 B2	10/2010	Hasenzahl et al.
5,985,850 A	11/1999	Falk et al.	7,829,116 B2	11/2010	Griswold et al.
5,989,568 A	11/1999	Breton et al.	7,850,992 B2	12/2010	Kim et al.
6,007,835 A	12/1999	Bon Lapillonne et al.	7,854,753 B2	12/2010	Kraft et al.
6,010,715 A	1/2000	Wick et al.	7,871,643 B2	1/2011	Lizio et al.
6,013,276 A	1/2000	Math et al.	7,960,368 B2	6/2011	Nickisch et al.
6,024,974 A	2/2000	Li	8,048,017 B2	11/2011	Xu
6,030,948 A	2/2000	Mann	8,063,030 B2	11/2011	Ellman
6,040,340 A	3/2000	Chwalisz et al.	8,071,576 B2	12/2011	Coelingh Bennink et al.
6,068,853 A	5/2000	Giannos et al.	8,075,916 B2	12/2011	Song et al.
6,087,352 A	7/2000	Trout	8,075,917 B2	12/2011	Chung et al.
6,090,404 A	7/2000	Meconi et al.	8,076,317 B2	12/2011	Kulmann
6,106,848 A	8/2000	Preu닐 et al.	8,080,553 B2	12/2011	Keith et al.
6,124,362 A	9/2000	Bradbury et al.	8,096,940 B2	1/2012	Josephson et al.
6,139,868 A	10/2000	Hoffmann	8,114,152 B2	2/2012	Furst
6,149,935 A	11/2000	Chiang et al.	8,114,442 B2	2/2012	Tucker et al.
6,187,323 B1	2/2001	Aiache et al.	8,119,741 B2	2/2012	Pavlín
6,217,886 B1	4/2001	Onyuksel et al.	8,124,118 B2	2/2012	Lennernas et al.
6,225,297 B1	5/2001	Stockemann et al.	8,124,595 B2	2/2012	Boissonneault
6,228,383 B1	5/2001	Hansen et al.	8,147,561 B2	4/2012	Binmoeller
6,228,852 B1	5/2001	Shaak	8,148,546 B2	4/2012	Schuster et al.
6,242,509 B1	6/2001	Berger et al.	8,158,613 B2	4/2012	Staniforth et al.
6,245,811 B1	6/2001	Horrobin et al.	8,163,722 B2	4/2012	Savoir et al.
6,267,984 B1	7/2001	Beste et al.	8,177,449 B2	5/2012	Bayly et al.
6,274,165 B1	8/2001	Meconi et al.	8,187,615 B2	5/2012	Friedman
6,303,132 B1	10/2001	Nelson	8,195,403 B2	6/2012	Ishikawa et al.
6,303,588 B1	10/2001	Danielov	8,221,785 B2	7/2012	Chien
6,312,703 B1	11/2001	Orthoefer	8,222,237 B2	7/2012	Nickisch et al.
6,328,987 B1	12/2001	Marini	8,257,724 B2	9/2012	Cromack et al.
6,344,211 B1	2/2002	Hille	8,257,725 B2	9/2012	Cromack et al.
6,372,245 B1	4/2002	Bowman et al.	8,268,352 B2	9/2012	Vaya et al.
6,420,352 B1	7/2002	Knowles	8,268,806 B2	9/2012	Labrie
6,432,438 B1	8/2002	Shukla	8,268,878 B2	9/2012	Armer et al.
6,451,300 B1	9/2002	Dunlop et al.	8,288,366 B2	10/2012	Chochinov et al.
6,465,004 B1	10/2002	Rossi Montero et al.	8,318,898 B2	11/2012	Fasel et al.
6,465,005 B1	10/2002	Biali et al.	8,324,193 B2	12/2012	Lee-Sepsick et al.
6,465,006 B1	10/2002	Zhang et al.	8,337,814 B2	12/2012	Osbakken et al.
6,495,160 B2	12/2002	Esposito et al.	8,344,007 B2	1/2013	Tang et al.
6,521,250 B2	2/2003	Meconi et al.	8,353,863 B2	1/2013	Imran
6,531,149 B1	3/2003	Kirstgen et al.	8,357,723 B2	1/2013	Satyam
6,538,039 B2	3/2003	Laurent	8,361,995 B2	1/2013	Schramm
6,548,053 B1	4/2003	Stewart et al.	8,362,091 B2	1/2013	Tamarkin et al.
6,555,131 B1	4/2003	Wolff et al.	8,372,424 B2	2/2013	Berry et al.
6,562,367 B1	5/2003	Wolff et al.	8,372,806 B2	2/2013	Boehler et al.
6,562,370 B2	5/2003	Luo et al.	8,377,482 B2	2/2013	Laurie et al.
6,562,790 B2	5/2003	Chein	8,377,994 B2	2/2013	Gray et al.
6,599,519 B1	7/2003	Seo et al.	8,394,759 B2	3/2013	Barathur et al.
6,610,674 B1	8/2003	Schreiber	8,415,332 B2	4/2013	Diliberti et al.
6,635,274 B1	10/2003	Masiz et al.	8,435,972 B2	5/2013	Stein et al.
6,638,528 B1	10/2003	Kanios	8,449,879 B2	5/2013	Laurent Applegate et al.
6,649,155 B1	11/2003	Dunlop et al.	8,450,108 B2	5/2013	Boyce
6,682,757 B1	1/2004	Wright	8,454,945 B2	6/2013	McCook et al.
6,708,822 B1	3/2004	Muni	8,455,468 B2	6/2013	Hoffman et al.
6,720,001 B2	4/2004	Chen et al.	8,461,138 B2	6/2013	Boissonneault
6,743,448 B2	6/2004	Kryger	8,476,252 B2	7/2013	Achleitner et al.
6,750,291 B2	6/2004	Kim et al.	8,481,488 B2	7/2013	Carter
6,821,524 B2	11/2004	Marini	8,486,374 B2	7/2013	Tamarkin et al.
6,911,211 B2	6/2005	Eini et al.	8,486,442 B2	7/2013	Matsushita et al.
6,960,337 B2	11/2005	Daniels et al.	8,492,368 B2	7/2013	Vanlandingham et al.
6,974,569 B2	12/2005	Dunlop et al.	8,507,467 B2	8/2013	Matsui et al.
6,995,149 B1	2/2006	Endrikat et al.	8,512,693 B2	8/2013	Capito et al.
7,004,321 B1	2/2006	Palm et al.	8,512,754 B2	8/2013	Needham
7,030,104 B2	4/2006	Gray et al.	8,518,376 B2	8/2013	Tamarkin et al.
			8,536,159 B2	9/2013	Li et al.
			8,540,967 B2	9/2013	Barrett et al.
			8,541,400 B2	9/2013	Johnsson et al.
			8,551,462 B2	10/2013	Goldstein et al.

US 8,993,548 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

8,557,281	B2	10/2013	Halliday et al.	2005/0186141	A1	8/2005	Gonda et al.
8,568,374	B2	10/2013	De Graaff et al.	2005/0196434	A1	9/2005	Briere
8,591,951	B2	11/2013	Kohn et al.	2005/0220900	A1	10/2005	Popp et al.
8,613,951	B2	12/2013	Zale et al.	2005/0239747	A1	10/2005	Yang et al.
8,633,178	B2	1/2014	Bernick et al.	2005/0239758	A1	10/2005	Roby
8,633,180	B2	1/2014	Li et al.	2005/0244360	A1	11/2005	Billoni
8,636,787	B2	1/2014	Sabaria	2005/0266088	A1	12/2005	Hinrichs et al.
8,636,982	B2	1/2014	Tamarkin et al.	2005/0271597	A1	12/2005	Keith
8,653,129	B2	2/2014	Fein et al.	2005/0272685	A1	12/2005	Hung
8,658,627	B2	2/2014	Voskuhl	2006/0009428	A1	1/2006	Grubb et al.
8,663,692	B1	3/2014	Mueller et al.	2006/0034904	A1	2/2006	Weimann
8,663,703	B2	3/2014	Lerner et al.	2006/0078618	A1	4/2006	Constantinides et al.
8,664,207	B2	3/2014	Li et al.	2006/0084704	A1	4/2006	Shih et al.
8,669,293	B2	3/2014	Levy et al.	2006/0088580	A1	4/2006	Meconi et al.
8,679,552	B2	3/2014	Guthery	2006/0100180	A1	5/2006	Nubbemeyer et al.
8,697,127	B2	4/2014	Sah	2006/0121102	A1	6/2006	Chiang
8,697,710	B2	4/2014	Li et al.	2006/0165744	A1	7/2006	Jamil et al.
8,703,105	B2	4/2014	Tamarkin et al.	2006/0193789	A1	8/2006	Tamarkin et al.
8,709,385	B2	4/2014	Tamarkin et al.	2006/0233743	A1	10/2006	Kelly
8,709,451	B2	4/2014	Nam et al.	2006/0233841	A1	10/2006	Brodbeck et al.
8,715,735	B2	5/2014	Funke et al.	2006/0246122	A1	11/2006	Langguth et al.
8,721,331	B2	5/2014	Raghuprasad	2006/0247221	A1	11/2006	Coelingh Bennink et al.
8,722,021	B2	5/2014	Friedman et al.	2006/0251581	A1	11/2006	McIntyre et al.
8,734,846	B2	5/2014	Ali et al.	2006/0275218	A1	12/2006	Tamarkin et al.
8,735,381	B2	5/2014	Podolski	2006/0276414	A1	12/2006	Coelingh Bennink et al.
8,741,336	B2	6/2014	Dipierro et al.	2006/0292223	A1	12/2006	Woolfson et al.
8,741,373	B2	6/2014	Bromley et al.	2007/0009559	A1	1/2007	Li et al.
8,753,661	B2	6/2014	Steinmueller Nethl et al.	2007/0009594	A1	1/2007	Grubb et al.
8,784,882	B2	7/2014	Mattern	2007/0010550	A1	1/2007	McKenzie
2001/0009673	A1	7/2001	Lipp et al.	2007/0014839	A1	1/2007	Bracht
2001/0023261	A1	9/2001	Ryoo et al.	2007/0015698	A1	1/2007	Kleinman et al.
2001/0053383	A1	12/2001	Miranda et al.	2007/0037780	A1	2/2007	Ebert et al.
2002/0035070	A1	3/2002	Gardlik et al.	2007/0037782	A1	2/2007	Hibino et al.
2002/0119174	A1	8/2002	Gardlik et al.	2007/0078091	A1	4/2007	Hubler et al.
2002/0119198	A1	8/2002	Gao et al.	2007/0128263	A1	6/2007	Gargiulo et al.
2002/0142017	A1	10/2002	Simonnet	2007/0154533	A1	7/2007	Dudley
2002/0169205	A1	11/2002	Chwalisz et al.	2007/0167418	A1	7/2007	Ferguson
2002/0193758	A1	12/2002	Sandberg	2007/0185068	A1	8/2007	Ferguson et al.
2002/0197286	A1	12/2002	Brandman et al.	2007/0190022	A1	8/2007	Bacopoulos et al.
2003/0003139	A1	1/2003	Lipp et al.	2007/0196415	A1	8/2007	Chen et al.
2003/0027772	A1	2/2003	Breton	2007/0232574	A1	10/2007	Galey et al.
2003/0044453	A1	3/2003	Dittgen et al.	2007/0248658	A1	10/2007	Zurdo Schroeder et al.
2003/0091620	A1	5/2003	Fikstad et al.	2007/0254858	A1	11/2007	Cronk
2003/0109507	A1	6/2003	Franke et al.	2007/0255197	A1	11/2007	Humberstone et al.
2003/0113268	A1	6/2003	Buenafae et al.	2007/0287688	A1	12/2007	Chan et al.
2003/0170295	A1	9/2003	Kim et al.	2007/0292359	A1	12/2007	Friedman et al.
2003/0175329	A1	9/2003	Azarnoff et al.	2007/0292461	A1	12/2007	Tamarkin et al.
2003/0175333	A1	9/2003	Shefer et al.	2007/0294293	A1	12/2007	Briere
2003/0219402	A1	11/2003	Rutter	2007/0298089	A1	12/2007	Saeki et al.
2003/0225047	A1	12/2003	Caubel et al.	2008/0026040	A1	1/2008	Farr et al.
2003/0225048	A1	12/2003	Caubel et al.	2008/0038219	A1	2/2008	Mosbaugh et al.
2003/0235596	A1	12/2003	Gao et al.	2008/0039405	A1	2/2008	Langley et al.
2003/0236236	A1	12/2003	Chen et al.	2008/0050317	A1	2/2008	Tamarkin et al.
2004/0022820	A1	2/2004	Anderson	2008/0051351	A1	2/2008	Ghisalberti
2004/0039356	A1	2/2004	Maki et al.	2008/0063607	A1	3/2008	Tamarkin et al.
2004/0043043	A1	3/2004	Schlyter et al.	2008/0069779	A1	3/2008	Tamarkin et al.
2004/0048900	A1	3/2004	Flood	2008/0069791	A1	3/2008	Beissert
2004/0087564	A1	5/2004	Wright et al.	2008/0095831	A1	4/2008	Mc Graw
2004/0092494	A9	5/2004	Dudley	2008/0138390	A1	6/2008	Hsu et al.
2004/0110732	A1	6/2004	Masini Eteve et al.	2008/0139392	A1	6/2008	Acosta Zara et al.
2004/0138103	A1	7/2004	Patt	2008/0153789	A1	6/2008	Dmowski et al.
2004/0146539	A1	7/2004	Gupta	2008/0175905	A1	7/2008	Liu et al.
2004/0161435	A1	8/2004	Gupta	2008/0175908	A1	7/2008	Liu et al.
2004/0191207	A1	9/2004	Lipari et al.	2008/0206156	A1	8/2008	Cronk
2004/0210280	A1	10/2004	Liedtke	2008/0206159	A1	8/2008	Tamarkin et al.
2004/0219124	A1	11/2004	Gupta	2008/0214512	A1	9/2008	Seitz et al.
2004/0225140	A1	11/2004	Fernandez et al.	2008/0226698	A1	9/2008	Tang et al.
2004/0241219	A1	12/2004	Hille et al.	2008/0227763	A1	9/2008	Lanquetin et al.
2005/0003003	A1	1/2005	Basu et al.	2008/0234240	A1	9/2008	Duesterberg et al.
2005/0014729	A1	1/2005	Pulaski	2008/0261931	A1	10/2008	Hedner et al.
2005/0020550	A1	1/2005	Morris et al.	2009/0004246	A1	1/2009	Woolfson et al.
2005/0054991	A1	3/2005	Tobyn et al.	2009/0010968	A1	1/2009	Allart et al.
2005/0118244	A1	6/2005	Theobald et al.	2009/0011041	A1	1/2009	Musaeva et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2009/0017120	A1	1/2009	Trimble et al.
2005/0152956	A1	7/2005	Dudley	2009/0022683	A1	1/2009	Song et al.
				2009/0047357	A1	2/2009	Tomohira et al.
				2009/0060997	A1	3/2009	Seitz et al.
				2009/0081206	A1	3/2009	Leibovitz
				2009/0093440	A1	4/2009	Murad

US 8,993,548 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2009/0098069 A1	4/2009 Vacca	2012/0129773 A1	5/2012 Geier et al.			
2009/0099149 A1	4/2009 Liu et al.	2012/0129819 A1	5/2012 Vancaillie et al.			
2009/0130029 A1	5/2009 Tamarkin et al.	2012/0136013 A1	5/2012 Li et al.			
2009/0175799 A1	7/2009 Tamarkin et al.	2012/0142645 A1	6/2012 Marx			
2009/0186081 A1	7/2009 Holm et al.	2012/0148670 A1	6/2012 Kim et al.			
2009/0197843 A1	8/2009 Notelovitz et al.	2012/0172343 A1	7/2012 Lindenthal et al.			
2009/0203658 A1	8/2009 Marx et al.	2012/0184515 A1	7/2012 Klar et al.			
2009/0227550 A1	9/2009 Mattern	2012/0231052 A1	9/2012 Sitruk Ware et al.			
2009/0285869 A1	11/2009 Trimble	2012/0232011 A1	9/2012 Kneissel et al.			
2009/0324714 A1	12/2009 Liu et al.	2012/0232042 A1	9/2012 Klar et al.			
2010/0008985 A1	1/2010 Pellikaan et al.	2012/0263679 A1	10/2012 Marlow et al.			
2010/0034838 A1	2/2010 Staniforth et al.	2012/0277249 A1	11/2012 Andersson et al.			
2010/0034880 A1	2/2010 Sintov et al.	2012/0277727 A1	11/2012 Doshi et al.			
2010/0055138 A1	3/2010 Margulies et al.	2012/0295911 A1	11/2012 Mannion et al.			
2010/0086501 A1	4/2010 Chang et al.	2012/0301517 A1	11/2012 Zhang et al.			
2010/0119585 A1	5/2010 Hille et al.	2012/0301538 A1	11/2012 Gordon Beresford et al.			
2010/0143420 A1	6/2010 Shenoy et al.	2012/0302535 A1	11/2012 Caufriez et al.			
2010/0143481 A1	6/2010 Shenoy et al.	2012/0316130 A1	12/2012 Hendrix			
2010/0150993 A1	6/2010 Theobald et al.	2012/0316496 A1	12/2012 Hoffmann et al.			
2010/0204326 A1	8/2010 D Souza	2012/0321579 A1	12/2012 Edelson et al.			
2010/0210994 A1	8/2010 Zarif	2012/0322779 A9	12/2012 Voskuhl			
2010/0221195 A1	9/2010 Tamarkin et al.	2012/0328549 A1	12/2012 Edelson et al.			
2010/0227797 A1	9/2010 Axelson et al.	2012/0329738 A1	12/2012 Liu			
2010/0247482 A1	9/2010 Cui et al.	2013/0004619 A1	1/2013 Chow et al.			
2010/0247635 A1	9/2010 Rosenberg et al.	2013/0011342 A1	1/2013 Tamarkin et al.			
2010/0273730 A1	10/2010 Hsu et al.	2013/0017239 A1	1/2013 Viladot Petit et al.			
2010/0278759 A1	11/2010 Murad	2013/0023505 A1	1/2013 Garfield et al.			
2010/0279988 A1	11/2010 Setiawan et al.	2013/0023823 A1	1/2013 Simpson et al.			
2010/0291191 A1	11/2010 Shoichet et al.	2013/0028850 A1	1/2013 Tamarkin et al.			
2010/0292199 A1	11/2010 Leverd et al.	2013/0029957 A1	1/2013 Giliyar et al.			
2010/0322884 A1	12/2010 Dipietro et al.	2013/0045266 A1	2/2013 Choi et al.			
2011/0039814 A1	2/2011 Huatan et al.	2013/0045953 A1	2/2013 Sitruk Ware et al.			
2011/0087192 A1	4/2011 Uhland et al.	2013/0059795 A1	3/2013 Lo et al.			
2011/0098258 A1	4/2011 Masini Eteve et al.	2013/0064897 A1	3/2013 Binay			
2011/0104268 A1	5/2011 Pachot et al.	2013/0072466 A1	3/2013 Choi et al.			
2011/0130372 A1	6/2011 Agostinacchio et al.	2013/0084257 A1	4/2013 Ishida et al.			
2011/0142945 A1	6/2011 Chen et al.	2013/0085123 A1	4/2013 Li et al.			
2011/0152840 A1	6/2011 Lee et al.	2013/0089574 A1	4/2013 Schmidt Gollwitzer et al.			
2011/0158920 A1	6/2011 Morley et al.	2013/0090318 A1	4/2013 Ullmann et al.			
2011/0171140 A1	7/2011 Illum et al.	2013/0102781 A1	4/2013 Bevill et al.			
2011/0190201 A1	8/2011 Hyde et al.	2013/0108551 A1	5/2013 Langereis et al.			
2011/0195031 A1	8/2011 Du	2013/0116215 A1	5/2013 Coma et al.			
2011/0238003 A1	9/2011 Bruno Raimondi et al.	2013/0131027 A1	5/2013 Arnold et al.			
2011/0244043 A1	10/2011 Xu et al.	2013/0131028 A1	5/2013 Abidi et al.			
2011/0250256 A1	10/2011 Hyun Oh et al.	2013/0131029 A1	5/2013 Bakker et al.			
2011/0250259 A1	10/2011 Buckman	2013/0149314 A1	6/2013 Bullerdiek et al.			
2011/0262373 A1	10/2011 Umbert Millet	2013/0164225 A1	6/2013 Tamarkin et al.			
2011/0275584 A1	11/2011 Wilckens et al.	2013/0164346 A1	6/2013 Lee et al.			
2011/0281832 A1	11/2011 Li et al.	2013/0165744 A1	6/2013 Carson et al.			
2011/0287094 A1	11/2011 Penhasi et al.	2013/0178452 A1	7/2013 King			
2011/0294738 A1	12/2011 Ren et al.	2013/0183254 A1	7/2013 Zhou et al.			
2011/0300167 A1	12/2011 McMurry et al.	2013/0183325 A1	7/2013 Bottoni et al.			
2011/0301087 A1	12/2011 McBride et al.	2013/0189193 A1	7/2013 Tamarkin et al.			
2011/0306579 A1	12/2011 Stein	2013/0189196 A1	7/2013 Tamarkin et al.			
2011/0318405 A1	12/2011 Erwin	2013/0189230 A1	7/2013 Shoichet et al.			
2011/0318431 A1	12/2011 Gulati	2013/0189368 A1	7/2013 Mosqueira et al.			
2012/0021041 A1	1/2012 Rossi et al.	2013/0210709 A1	8/2013 McMurry et al.			
2012/0028888 A1	2/2012 Janz et al.	2013/0216550 A1	8/2013 Penninger et al.			
2012/0028910 A1	2/2012 Combal et al.	2013/0216596 A1	8/2013 Viladot Petit et al.			
2012/0028936 A1	2/2012 Gloger et al.	2013/0224177 A1	8/2013 Kim et al.			
2012/0046264 A1	2/2012 Simes et al.	2013/0224257 A1	8/2013 Sah et al.			
2012/0046518 A1	2/2012 Yoakum et al.	2013/0224268 A1	8/2013 Alam et al.			
2012/0058171 A1	3/2012 De Graaff et al.	2013/0224300 A1	8/2013 Maggio			
2012/0058962 A1	3/2012 Cumming et al.	2013/0225412 A1	8/2013 Sardari Lodriche et al.			
2012/0058979 A1	3/2012 Keith et al.	2013/0225542 A1	8/2013 Poegh et al.			
2012/0064135 A1	3/2012 Levin et al.	2013/0226113 A1	8/2013 Schumacher et al.			
2012/0065179 A1	3/2012 Andersson	2013/0243696 A1	9/2013 Wang et al.			
2012/0087872 A1	4/2012 Tamarkin et al.	2013/0245253 A1	9/2013 Marx et al.			
2012/0101073 A1	4/2012 Mannion et al.	2013/0245570 A1	9/2013 Jackson			
2012/0121517 A1	5/2012 Song et al.	2013/0261096 A1	10/2013 Merian et al.			
2012/0121692 A1	5/2012 Xu et al.	2013/0266645 A1	10/2013 Becker et al.			
2012/0122829 A1	5/2012 Taravella et al.	2013/0267485 A1	10/2013 Da Silva Maia Filho			
2012/0128654 A1	5/2012 Terpstra et al.	2013/0273167 A1	10/2013 Lee et al.			
2012/0128683 A1	5/2012 Shantha	2013/0274211 A1	10/2013 Burman et al.			
2012/0128733 A1	5/2012 Perrin et al.					

US 8,993,548 B2

Page 5

(56)

References Cited

U.S. PATENT DOCUMENTS

2013/0280213	A1	10/2013	Voskuhl
2013/0316374	A1	11/2013	Penninger et al.
2013/0317065	A1	11/2013	Tatani et al.
2013/0317315	A1	11/2013	Lu et al.
2013/0324565	A1	12/2013	Li et al.
2013/0331363	A1	12/2013	Li et al.
2013/0338124	A1	12/2013	Li et al.
2013/0345187	A1	12/2013	Rodriguez Oquendo
2014/0018335	A1	1/2014	Tatani et al.
2014/0024590	A1	1/2014	Weidhaas et al.
2014/0031289	A1	1/2014	Song et al.
2014/0031323	A1	1/2014	Perez
2014/0066416	A1	3/2014	Leunis et al.
2014/0072531	A1	3/2014	Kim et al.
2014/0079686	A1	3/2014	Barman et al.
2014/0088058	A1	3/2014	Maurizio
2014/0088059	A1	3/2014	Perumal et al.
2014/0094426	A1	4/2014	Drummond et al.
2014/0100159	A1	4/2014	Conrad
2014/0100206	A1	4/2014	Bernick et al.
2014/0113889	A1	4/2014	Connor et al.
2014/0127185	A1	5/2014	Stein et al.
2014/0127280	A1	5/2014	Duesterberg et al.
2014/0127308	A1	5/2014	Opara et al.
2014/0128798	A1	5/2014	Janson et al.
2014/0148491	A1	5/2014	Valía et al.
2014/0186332	A1	7/2014	Ezrin et al.
2014/0187487	A1	7/2014	Shoichet et al.
2014/0193523	A1	7/2014	Henry
2014/0194396	A1	7/2014	Li et al.
2014/0206616	A1	7/2014	Ko et al.

FOREIGN PATENT DOCUMENTS

WO	WO03028667	4/2003
WO	WO2004014432	2/2004
WO	WO2005081825	9/2005
WO	WO2007120868	10/2007
WO	WO2010146872	12/2010
WO	WO2012055814	A1 5/2012
WO	WO2012055840	A1 5/2012
WO	WO2012065740	5/2012
WO	WO2012098090	A1 7/2012
WO	WO2012116277	A1 8/2012
WO	WO2012118563	A2 9/2012
WO	WO2012120365	A1 9/2012
WO	WO2012127501	A2 9/2012
WO	WO2012156561	A1 11/2012
WO	WO2012156822	A1 11/2012
WO	WO2012158483	A2 11/2012
WO	WO2012166909	A1 12/2012
WO	WO2012170578	A1 12/2012
WO	WO2013011501	A1 1/2013
WO	WO2013025449	A1 2/2013
WO	WO2013028639	A1 2/2013
WO	WO2013035101	A1 3/2013
WO	WO2013044067	A1 3/2013

WO	WO2013045404	A2 4/2013
WO	WO2013059285	A1 4/2013
WO	WO2013063279	A1 5/2013
WO	WO2013064620	A1 5/2013
WO	WO2013071281	A1 5/2013
WO	WO2013088254	6/2013
WO	WO2013102665	A1 7/2013
WO	WO2013106437	A1 7/2013
WO	WO2013113690	8/2013
WO	WO2013124415	A1 8/2013
WO	WO2013127727	A1 9/2013
WO	WO2013127728	A1 9/2013
WO	WO2013144356	A1 10/2013
WO	WO2013149258	A2 10/2013
WO	WO2013158454	A2 10/2013
WO	WO2013170052	A1 11/2013
WO	WO2013178587	A1 12/2013
WO	WO2014001904	A1 1/2014
WO	WO2014004424	A1 1/2014
WO	WO2014009434	A1 1/2014
WO	WO2014018569	A1 1/2014
WO	WO2014018570	A1 1/2014
WO	WO2014018571	A2 1/2014
WO	WO2014018856	A1 1/2014
WO	WO2014018932	A2 1/2014
WO	WO2014031958	A1 2/2014
WO	WO2014041120	A1 3/2014
WO	WO2014052792	A1 4/2014
WO	WO2014056897	A1 4/2014
WO	WO2014066442	A2 5/2014
WO	WO2014074846	A1 5/2014
WO	WO2014076231	A1 5/2014
WO	WO2014076569	A2 5/2014
WO	WO2014081598	A1 5/2014
WO	WO2014086739	A1 6/2014
WO	WO2014093114	A1 6/2014
WO	WO2014104784	A1 7/2014

OTHER PUBLICATIONS

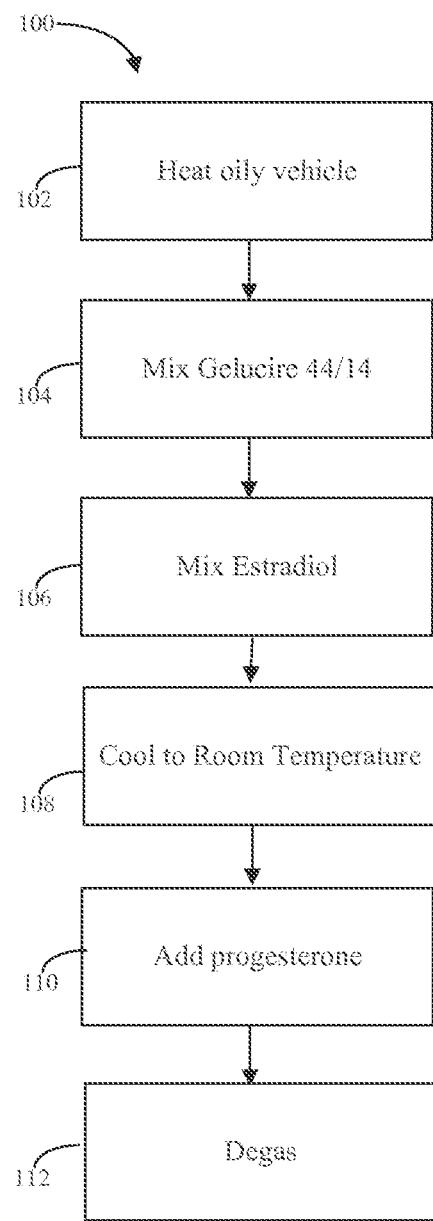
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.

* cited by examiner

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US 8,993,548 B2**Fig. 1**

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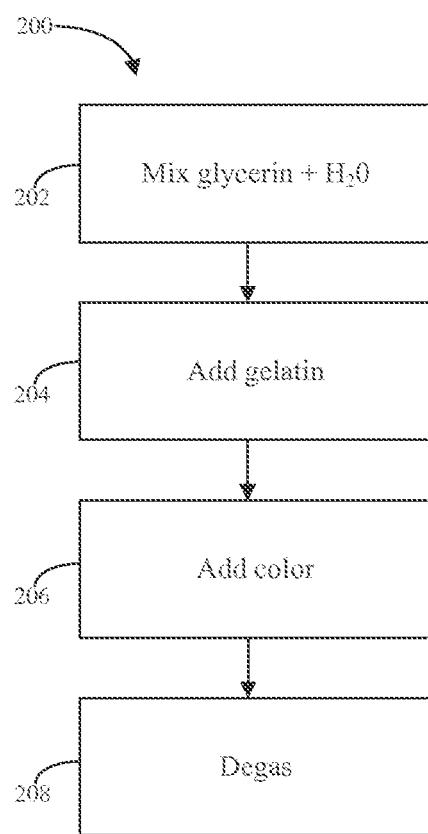


Fig. 2

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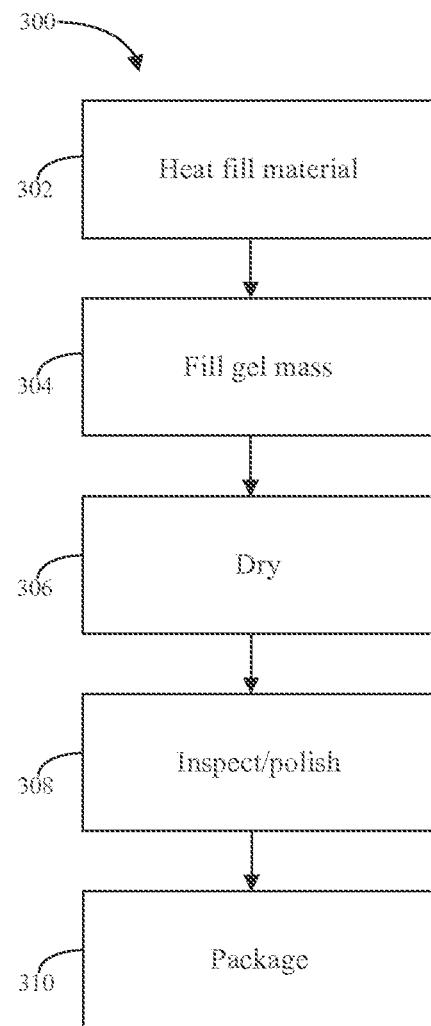


Fig. 3

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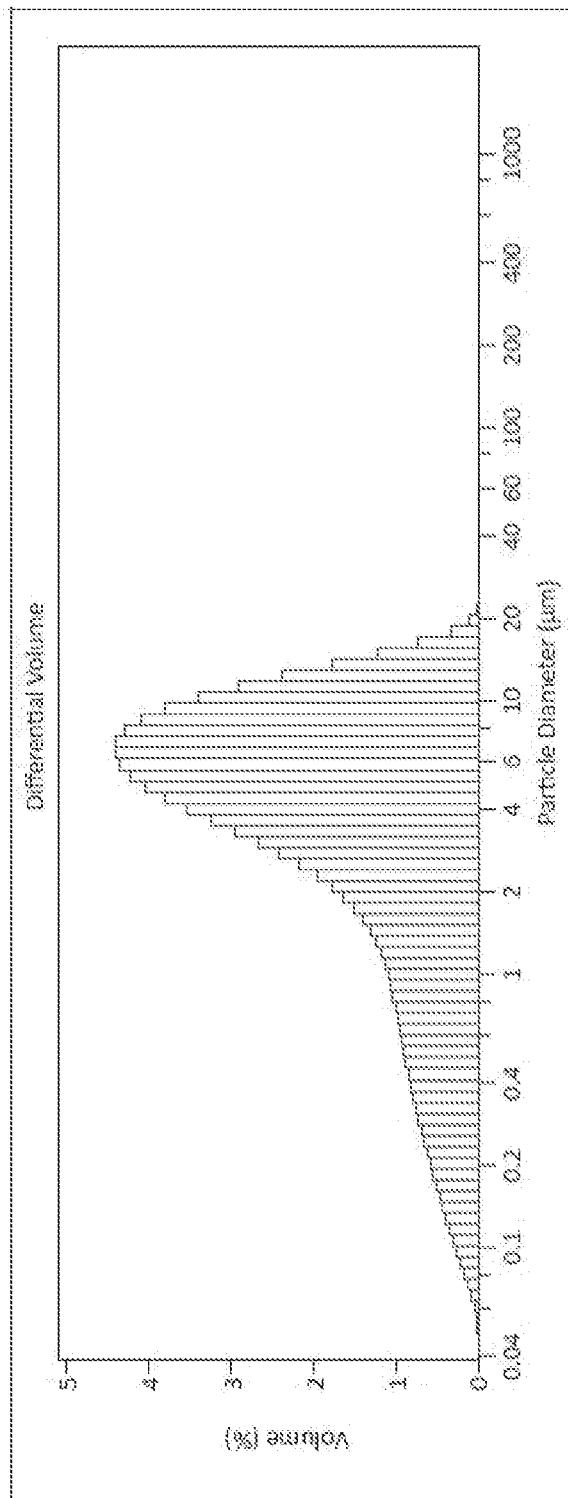


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCES TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which application claims priority to the following U.S. Provisional patent applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

35 SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via 40 pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, 45 each in accordance with the invention are set forth below.

50 BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated 55 herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

65 FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pk) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max}, and optionally, T_{max}.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, "C_{max}" as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, "T_{max}" as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating

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pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. Description and Preferred Embodiments

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra-

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and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

5 These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

10 Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

15 Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction 20 Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

25 The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm . The ULM is a liquid based 30 module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may 35 be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other 40 suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the 45 Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. 50 Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

55 The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may 60 use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These 65 formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other

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solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may

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contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and

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filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference—Salo, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

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Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/ triglycerides of caprylic/ capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Myglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/-2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Cap- sule (mg)	% w/w	Qty/Cap- sule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/di- glycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32- glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier

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with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an $\times 75$ of 17.3 μm , and an $\times 25$ of 5.3 μm . The Beckman Device also yielded that the mean particle size is 11.8 μm , the median particle size is 11.04 μm , the mode particle size is 13.6 μm , and the standard deviation is 7.8 μm .

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Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules				
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03
3.	Capmul MCM, NF		82.57	577.97
4.	Gelucire 44/14, NF		10.0	70.00
Total:		100.00	700.00	7.00

TABLE 14-continued

Ingredient	%	mg/ Capsule	Function
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

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For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an $\times 75$ of 7.442 μm , and an $\times 25$ of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 4.

Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed

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An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:		100.00	200.00	mg 2000.00	

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
	Total:	100.00		600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout

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the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE®(Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA-vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator,

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or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of

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FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant.

Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical formulation comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent; wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed; wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and wherein the solubilizing agent comprises an effective amount of a C6-C12 oil.

2. The pharmaceutical formulation of claim 1, further comprising partially solubilized progesterone.

3. The pharmaceutical formulation of claim 1, wherein the formulation is contained within a gelatin capsule.

4. The pharmaceutical formulation of claim 1, wherein the medium chain solubilizing agent is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

5. The pharmaceutical formulation of claim , wherein said estradiol has a dosage strength at least about 0.125 mg and wherein said progesterone has a dosage strength at least about 25 mg.

6. The pharmaceutical formulation of claim 1, wherein the ratio of progesterone to estradiol is at least 95:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,993,548 B2
APPLICATION NO. : 14/475814
DATED : March 31, 2015
INVENTOR(S) : Brian A. Bernick et al.

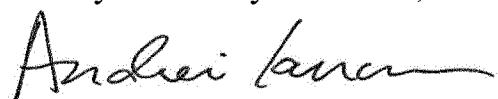
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT F



US008993549B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** **US 8,993,549 B2**
(45) **Date of Patent:** ***Mar. 31, 2015**

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Neda Irani**, Palm Beach Garden, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/475,864**(22) Filed: **Sep. 3, 2014**(65) **Prior Publication Data**

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(60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

(51) **Int. Cl.**

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(52) **U.S. Cl.**

CPC . *A61K 31/57* (2013.01); *A61K 9/16* (2013.01);
A61K 31/565 (2013.01); *A61K 9/4858* (2013.01); *A61K 9/7023* (2013.01)

USPC **514/169; 424/452**(58) **Field of Classification Search**

CPC A61K 31/57; A61K 31/565

USPC **514/169; 424/452**

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,232,438 A	2/1941	Butenandt
4,900,734 A *	2/1990	Maxson et al. 514/171
5,538,736 A	7/1996	Barth et al.
5,556,635 A	9/1996	Grognet et al.
5,580,572 A	12/1996	Liorzou et al.
5,605,702 A	2/1997	Math et al.
5,607,691 A	3/1997	Solas et al.
5,607,693 A	3/1997	Bonte et al.
5,609,617 A	3/1997	Cady et al.
5,626,866 A	5/1997	Heiber et al.
5,653,983 A	8/1997	Bonte et al.
5,660,839 A	8/1997	Allec et al.
5,662,927 A	9/1997	Ehrlich et al.
5,663,160 A	9/1997	Dumas et al.
5,686,097 A	11/1997	Crisologo et al.
5,693,335 A	12/1997	Xia et al.
5,700,480 A	12/1997	Hille et al.
5,719,197 A	2/1998	Mantelle et al.
5,770,220 A	6/1998	Meconi et al.
5,770,227 A	6/1998	Dong et al.
5,780,044 A	7/1998	Tipton et al.
5,780,050 A	7/1998	Jain et al.
5,788,984 A	8/1998	Schmidt et al.
5,820,878 A	10/1998	Shimamura et al.
5,840,327 A	11/1998	Gale et al.
5,843,468 A	12/1998	Yum et al.
5,843,979 A	12/1998	Wille et al.
5,858,394 A	1/1999	Lipp et al.
5,863,552 A	1/1999	Yue

(Continued)

FOREIGN PATENT DOCUMENTS

WO	WO9619975	7/1996
WO	WO20141878	5/2002

(Continued)

OTHER PUBLICATIONS

Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.

(Continued)

Primary Examiner — Dennis J Parad(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

US 8,993,549 B2

Page 2

(56)	References Cited					
U.S. PATENT DOCUMENTS						
5,882,676 A	3/1999	Yum et al.	7,094,228 B2	8/2006	Zhang et al.	
5,885,612 A	3/1999	Meconi et al.	7,097,853 B1	8/2006	Keister et al.	
5,888,533 A	3/1999	Dunn	7,105,573 B2	9/2006	Krajcik et al.	
5,891,462 A	4/1999	Carrara	7,153,522 B1	12/2006	Ikeura et al.	
5,902,603 A	5/1999	Chen et al.	7,175,850 B2	2/2007	Cevc	
5,904,931 A	5/1999	Gunther et al.	7,198,800 B1	4/2007	Ko	
5,906,830 A	5/1999	Farinas et al.	7,381,427 B2	6/2008	Ancira et al.	
5,912,010 A	6/1999	Wille et al.	7,456,159 B2	11/2008	Houze et al.	
5,919,477 A	7/1999	Bevan et al.	7,498,303 B2	3/2009	Arnold et al.	
5,942,243 A	8/1999	Shah	7,534,780 B2	5/2009	Ring et al.	
5,952,000 A	9/1999	Fikstad et al.	7,569,274 B2	8/2009	Alphonse et al.	
5,968,919 A	10/1999	Gyurik et al.	7,799,769 B2	9/2010	White et al.	
5,985,311 A	11/1999	Cordes et al.	7,815,936 B2	10/2010	Hasenzahl et al.	
5,985,850 A	11/1999	Falk et al.	7,829,116 B2	11/2010	Frye et al.	
5,989,568 A	11/1999	De Lacharriere et al.	7,850,992 B2	12/2010	Hwang, II et al.	
6,007,835 A	12/1999	Bon Lapillonne et al.	7,854,753 B2	12/2010	Kraft et al.	
6,010,715 A	1/2000	Pollock et al.	7,871,643 B2	1/2011	Lizio et al.	
6,013,276 A	1/2000	Teillaud et al.	7,960,368 B2	6/2011	Rao et al.	
6,024,974 A	2/2000	Li	8,048,017 B2	11/2011	Xu	
6,030,948 A	2/2000	Mann	8,063,030 B2	11/2011	Ellman	
6,040,340 A	3/2000	Garfield et al.	8,071,576 B2	12/2011	Visser et al.	
6,068,853 A	5/2000	Berner et al.	8,075,916 B2	12/2011	Park et al.	
6,087,352 A	7/2000	Trout	8,075,917 B2	12/2011	Park et al.	
6,090,404 A	7/2000	Meconi et al.	8,076,317 B2	12/2011	Kulmann	
6,106,848 A	8/2000	Willcox et al.	8,080,553 B2	12/2011	Auspitz et al.	
6,124,362 A	9/2000	Bradbury et al.	8,096,940 B2	1/2012	Iverson et al.	
6,139,868 A	10/2000	Hoffmann	8,114,152 B2	2/2012	Furst	
6,149,935 A	11/2000	Tenzel et al.	8,114,442 B2	2/2012	Tucker et al.	
6,187,323 B1	2/2001	Aiache et al.	8,119,741 B2	2/2012	Pavlín	
6,217,886 B1	4/2001	Rubinstein et al.	8,124,118 B2	2/2012	Lennernaes et al.	
6,225,297 B1	5/2001	Stockemann et al.	8,124,595 B2	2/2012	Boissonneault	
6,228,383 B1	5/2001	Hansen et al.	8,147,561 B2	4/2012	Binmoeller	
6,228,852 B1	5/2001	Shaak	8,148,546 B2	4/2012	Baasner et al.	
6,242,509 B1	6/2001	MacQueen et al.	8,158,613 B2	4/2012	Staniforth et al.	
6,245,811 B1	6/2001	Horrobin et al.	8,163,722 B2	4/2012	Savoir et al.	
6,267,984 B1	7/2001	Hamlin et al.	8,177,449 B2	5/2012	Watkinson et al.	
6,274,165 B1	8/2001	Meconi et al.	8,187,615 B2	5/2012	Friedman	
6,303,132 B1	10/2001	Nelson	8,195,403 B2	6/2012	Wood, Jr. et al.	
6,303,588 B1	10/2001	Danielov	8,221,785 B2	7/2012	Chien	
6,312,703 B1	11/2001	Orthoefer	8,222,237 B2	7/2012	Narkunan et al.	
6,328,987 B1	12/2001	Marini	8,257,724 B2	9/2012	Cromack et al.	
6,344,211 B1	2/2002	Hille et al.	8,257,725 B2	9/2012	Cromack et al.	
6,372,245 B1	4/2002	Vo et al.	8,268,352 B2	9/2012	Karan et al.	
6,420,352 B1	7/2002	Knowles	8,268,806 B2	9/2012	Labrie	
6,432,438 B1	8/2002	Shukla	8,268,878 B2	9/2012	Armer et al.	
6,451,300 B1	9/2002	Leyba et al.	8,288,366 B2	10/2012	Gonzalez et al.	
6,465,004 B1	10/2002	Houze et al.	8,318,898 B2	11/2012	Fasel et al.	
6,465,005 B1	10/2002	Biali et al.	8,324,193 B2	12/2012	Lee et al.	
6,465,006 B1	10/2002	Zhang et al.	8,337,814 B2	12/2012	Osbakken et al.	
6,495,160 B2	12/2002	Esposito et al.	8,344,007 B2	1/2013	Chui et al.	
6,521,250 B2	2/2003	Seibertz et al.	8,372,806 B2	2/2013	Bragagna et al.	
6,531,149 B1	3/2003	Meconi et al.	8,377,482 B2	2/2013	Laurie et al.	
6,538,039 B2	3/2003	Laurent	8,357,723 B2	1/2013	Satyam	
6,548,053 B1	4/2003	Murray et al.	8,361,995 B2	1/2013	Schramm	
6,555,131 B1	4/2003	Wolff et al.	8,362,091 B2	1/2013	Besonov et al.	
6,562,367 B1	5/2003	Wolff et al.	8,372,424 B2	2/2013	Berry et al.	
6,562,370 B2	5/2003	Luo et al.	8,435,972 B2	5/2013	Sayeed et al.	
6,562,790 B2	5/2003	Chein	8,449,879 B2	5/2013	Laurent et al.	
6,599,519 B1	7/2003	Seo et al.	8,450,108 B2	5/2013	Boyce	
6,610,674 B1	8/2003	Schreiber	8,454,945 B2	6/2013	Narain et al.	
6,635,274 B1	10/2003	Carter et al.	8,455,468 B2	6/2013	Kellerman et al.	
6,638,528 B1	10/2003	Kanios	8,461,138 B2	6/2013	Boissonneault	
6,649,155 B1	11/2003	Dunlop et al.	8,476,252 B2	7/2013	Pickersgill et al.	
6,682,757 B1	1/2004	Wright	8,481,488 B2	7/2013	Carter	
6,708,822 B1	3/2004	Muni	8,486,374 B2	7/2013	Zlatkis et al.	
6,720,001 B2	4/2004	Chen et al.	8,486,442 B2	7/2013	Yamaji et al.	
6,743,448 B2	6/2004	Kryger	8,492,368 B2	7/2013	Lewandowski et al.	
6,750,291 B2	6/2004	Kim et al.	8,507,467 B2	8/2013	Ueda et al.	
6,821,524 B2	11/2004	Marini	8,512,693 B2	8/2013	Azevedo et al.	
6,911,211 B2	6/2005	Tamarkin et al.	8,512,754 B2	8/2013	Needham	
6,960,337 B2	11/2005	Pike et al.	8,518,376 B2	8/2013	Schuz et al.	
6,974,569 B2	12/2005	Boyd et al.	8,536,159 B2	9/2013	Zeng et al.	
6,995,149 B1	2/2006	Reilhac et al.	8,540,967 B2	9/2013	Trivedi et al.	
7,004,321 B1	2/2006	Hackbarth et al.	8,541,400 B2	9/2013	Joabsson et al.	
7,030,104 B2	4/2006	Paris et al.	8,551,462 B2	10/2013	Marenus et al.	

US 8,993,549 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

8,557,281	B2	10/2013	Tuominen et al.	2005/0186141	A1	8/2005	Gonda et al.
8,568,374	B2	10/2013	De Graaff et al.	2005/0196434	A1	9/2005	Briere
8,591,951	B2	11/2013	Kohn et al.	2005/0220900	A1	10/2005	Wuttke et al.
8,613,951	B2	12/2013	Troiano et al.	2005/0239747	A1	10/2005	Le et al.
8,633,178	B2	1/2014	Cacace et al.	2005/0239758	A1	10/2005	Roby
8,633,180	B2	1/2014	Zeng et al.	2005/0244360	A1	11/2005	Billoni
8,636,787	B2	1/2014	Sabaria	2005/0266088	A1	12/2005	Frijlink et al.
8,636,982	B2	1/2014	Schuz et al.	2005/0271597	A1	12/2005	Keith
8,653,129	B2	2/2014	Fein et al.	2005/0272685	A1	12/2005	Hung
8,658,627	B2	2/2014	Voskuhl	2006/0009428	A1	1/2006	Grubb et al.
8,663,692	B1	3/2014	Mueller et al.	2006/0034904	A1	2/2006	Weimann
8,663,703	B2	3/2014	Moldavski et al.	2006/0078618	A1	4/2006	Constantinides et al.
8,664,207	B2	3/2014	Zheng et al.	2006/0084704	A1	4/2006	Shih et al.
8,669,293	B2	3/2014	Sharoni et al.	2006/0088580	A1	4/2006	Seibertz et al.
8,679,552	B2	3/2014	Guthery	2006/0100180	A1	5/2006	Bohlmann et al.
8,697,127	B2	4/2014	Sah	2006/0121102	A1	6/2006	Chiang
8,697,710	B2	4/2014	Zeng et al.	2006/0165744	A1	7/2006	Anyarambhatla et al.
8,703,105	B2	4/2014	Besonov et al.	2006/0193789	A1	8/2006	Tamarkin et al.
8,709,385	B2	4/2014	Schuz et al.	2006/0233743	A1	10/2006	Kelly
8,709,451	B2	4/2014	Rapoport et al.	2006/0233841	A1	10/2006	Pushpala et al.
8,715,735	B2	5/2014	Funke et al.	2006/0246122	A1	11/2006	Langguth et al.
8,721,331	B2	5/2014	Raghuprasad	2006/0247221	A1	11/2006	Coelingh et al.
8,722,021	B2	5/2014	Eini et al.	2006/0251581	A1	11/2006	Madenjian et al.
8,734,846	B2	5/2014	Hrkach et al.	2006/0275218	A1	12/2006	Besonov et al.
8,735,381	B2	5/2014	Podolski	2006/0276414	A1	12/2006	Coelingh et al.
8,741,336	B2	6/2014	Dipierro et al.	2006/0292223	A1	12/2006	Mc Ilroy et al.
8,741,373	B2	6/2014	Rao et al.	2007/0009559	A1	1/2007	Alosio et al.
8,753,661	B2	6/2014	Gassner et al.	2007/0009594	A1	1/2007	Grubb et al.
8,784,882	B2	7/2014	Mattern	2007/0010550	A1	1/2007	McKenzie
2001/0009673	A1	7/2001	Gunther et al.	2007/0014839	A1	1/2007	Bracht
2001/0023261	A1	9/2001	Ryoo et al.	2007/0015698	A1	1/2007	Goldstein et al.
2001/0053383	A1	12/2001	Sabotsky et al.	2007/0037780	A1	2/2007	Anigbogu et al.
2002/0035070	A1	3/2002	Gardlik et al.	2007/0037782	A1	2/2007	Suzuki et al.
2002/0119174	A1	8/2002	Gardlik et al.	2007/0078091	A1	4/2007	Hubler et al.
2002/0119198	A1	8/2002	Gao et al.	2007/0128263	A1	6/2007	Wall et al.
2002/0142017	A1	10/2002	Simonnet	2007/0154533	A1	7/2007	Dudley
2002/0169205	A1	11/2002	Garfield et al.	2007/0167418	A1	7/2007	Ferguson
2002/0193758	A1	12/2002	Sandberg	2007/0185068	A1	8/2007	Ferguson et al.
2002/0197286	A1	12/2002	Brandman et al.	2007/0190022	A1	8/2007	Chiao et al.
2003/0003139	A1	1/2003	Gunther et al.	2007/0196415	A1	8/2007	Houston et al.
2003/0027772	A1	2/2003	Breton	2007/0232574	A1	10/2007	Bernard et al.
2003/0044453	A1	3/2003	Volkel et al.	2007/0248658	A1	10/2007	Bracht et al.
2003/0091620	A1	5/2003	Venkateshwaran et al.	2007/0254858	A1	11/2007	Cronk
2003/0109507	A1	6/2003	Beckmann et al.	2007/0255197	A1	11/2007	Wilkins et al.
2003/0113268	A1	6/2003	Buenafae et al.	2007/0287688	A1	12/2007	Chan et al.
2003/0170295	A1	9/2003	Yoon et al.	2007/0292359	A1	12/2007	Schuz et al.
2003/0175329	A1	9/2003	Mak et al.	2007/0292461	A1	12/2007	Danziger et al.
2003/0175333	A1	9/2003	Shefer et al.	2007/0292493	A1	12/2007	Briere
2003/0219402	A1	11/2003	Rutter	2007/0298089	A1	12/2007	Yoshinaga et al.
2003/0225047	A1	12/2003	Friedman et al.	2008/0026040	A1	1/2008	Rivera et al.
2003/0225048	A1	12/2003	Friedman et al.	2008/0038219	A1	2/2008	Carlson et al.
2003/0235596	A1	12/2003	Gao et al.	2008/0039405	A1	2/2008	Joseph et al.
2003/0236236	A1	12/2003	Chen et al.	2008/0050317	A1	2/2008	Besonov et al.
2004/0022820	A1	2/2004	Anderson	2008/0051351	A1	2/2008	Ghisalberti
2004/0039356	A1	2/2004	Maki et al.	2008/0063607	A1	3/2008	Berman et al.
2004/0043043	A1	3/2004	Schlyter et al.	2008/0069779	A1	3/2008	Schuz et al.
2004/0048900	A1	3/2004	Flood	2008/0069791	A1	3/2008	Beissert
2004/0087564	A1	5/2004	Wright et al.	2008/0095831	A1	4/2008	Mc Graw
2004/0092494	A9	5/2004	Dudley	2008/0138390	A1	6/2008	Gricenko et al.
2004/0110732	A1	6/2004	Masini et al.	2008/0139392	A1	6/2008	Yuan et al.
2004/0138103	A1	7/2004	Patt	2008/0153789	A1	6/2008	Dmowski et al.
2004/0146539	A1	7/2004	Gupta	2008/0175905	A1	7/2008	Baksh et al.
2004/0161435	A1	8/2004	Gupta	2008/0175908	A1	7/2008	Baksh et al.
2004/0191207	A1	9/2004	Lipari et al.	2008/0206156	A1	8/2008	Cronk
2004/0210280	A1	10/2004	Liedtke	2008/0206159	A1	8/2008	Schuz et al.
2004/0219124	A1	11/2004	Gupta	2008/0214512	A1	9/2008	Seitz et al.
2004/0225140	A1	11/2004	Sciano et al.	2008/0226698	A1	9/2008	Beste et al.
2004/0241219	A1	12/2004	Hille et al.	2008/0227763	A1	9/2008	Paris et al.
2005/0003003	A1	1/2005	Deaver et al.	2008/0234240	A1	9/2008	Duesterberg et al.
2005/0014729	A1	1/2005	Pulaski	2008/0261931	A1	10/2008	Stenlof et al.
2005/0020550	A1	1/2005	Latif et al.	2009/0004246	A1	1/2009	Woolfson et al.
2005/0054991	A1	3/2005	Paterson et al.	2009/0010968	A1	1/2009	Peyrot et al.
2005/0118244	A1	6/2005	Theobald et al.	2009/0011041	A1	1/2009	Musaeva et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2009/0017120	A1	1/2009	Brisco et al.
2005/0152956	A1	7/2005	Dudley	2009/0022683	A1	1/2009	Park et al.
				2009/0047357	A1	2/2009	Tomohira et al.
				2009/0060997	A1	3/2009	Seitz et al.
				2009/0081206	A1	3/2009	Leibovitz
				2009/0093440	A1	4/2009	Murad

US 8,993,549 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2009/0098069 A1	4/2009 Vacca	2012/0129773 A1	5/2012 Geier et al.			
2009/0099149 A1	4/2009 Kresevic et al.	2012/0129819 A1	5/2012 Vancaillie et al.			
2009/0130029 A1	5/2009 Tamarkin et al.	2012/0136013 A1	5/2012 Wennogle et al.			
2009/0175799 A1	7/2009 Tamarkin et al.	2012/0142645 A1	6/2012 Marx			
2009/0186081 A1	7/2009 Slot et al.	2012/0148670 A1	6/2012 Lee et al.			
2009/0197843 A1	8/2009 Notelovitz et al.	2012/0172343 A1	7/2012 Schuermann et al.			
2009/0203658 A1	8/2009 Rose et al.	2012/0184515 A1	7/2012 Schwede et al.			
2009/0227550 A1	9/2009 Mattern	2012/0231052 A1	9/2012 Brinton et al.			
2009/0285869 A1	11/2009 Trimble	2012/0232011 A1	9/2012 Kneissel et al.			
2009/0324714 A1	12/2009 Kresevic et al.	2012/0232042 A1	9/2012 Krenz et al.			
2010/0008985 A1	1/2010 Vermeulen et al.	2012/0263679 A1	10/2012 Wallace et al.			
2010/0034838 A1	2/2010 Staniforth et al.	2012/0277249 A1	11/2012 Tarrand et al.			
2010/0034880 A1	2/2010 Sintov et al.	2012/0277727 A1	11/2012 Doshi et al.			
2010/0055138 A1	3/2010 Jacobs et al.	2012/0295911 A1	11/2012 Mannion et al.			
2010/0086501 A1	4/2010 Chang et al.	2012/0301517 A1	11/2012 Warner et al.			
2010/0119585 A1	5/2010 Hille et al.	2012/0301538 A1	11/2012 Latere et al.			
2010/0143420 A1	6/2010 Lee et al.	2012/0302535 A1	11/2012 Caufriez et al.			
2010/0143481 A1	6/2010 Shenoy et al.	2012/0316130 A1	12/2012 Hendrix			
2010/0150993 A1	6/2010 Theobald et al.	2012/0316496 A1	12/2012 Horres et al.			
2010/0204326 A1	8/2010 D'Souza	2012/0321579 A1	12/2012 Edelson et al.			
2010/0210994 A1	8/2010 Zarif	2012/0322779 A9	12/2012 Voskuhl			
2010/0221195 A1	9/2010 Ziv et al.	2012/0328549 A1	12/2012 Edelson et al.			
2010/0227797 A1	9/2010 Danielsson et al.	2012/0329738 A1	12/2012 Liu			
2010/0247482 A1	9/2010 Chen et al.	2013/0004619 A1	1/2013 Goh et al.			
2010/0247635 A1	9/2010 Schmidt et al.	2013/0011342 A1	1/2013 Hazot et al.			
2010/0273730 A1	10/2010 Hsu et al.	2013/0017239 A1	1/2013 Fernandez et al.			
2010/0278759 A1	11/2010 Murad	2013/0023505 A1	1/2013 Garfield et al.			
2010/0279988 A1	11/2010 Setiawan et al.	2013/0023823 A1	1/2013 Volland et al.			
2010/0291191 A1	11/2010 Lapitsky et al.	2013/0028850 A1	1/2013 Hazot et al.			
2010/0292199 A1	11/2010 Leverd et al.	2013/0029957 A1	1/2013 Venkateshwaran et al.			
2010/0322884 A1	12/2010 Wilkins et al.	2013/0045266 A1	2/2013 Kang et al.			
2011/0039814 A1	2/2011 Ross et al.	2013/0045953 A1	2/2013 Grenier et al.			
2011/0087192 A1	4/2011 Uhland et al.	2013/0059795 A1	3/2013 Lo et al.			
2011/0098258 A1	4/2011 Canet et al.	2013/0064897 A1	3/2013 Binay			
2011/0104268 A1	5/2011 Segot et al.	2013/0072466 A1	3/2013 Choi et al.			
2011/0130372 A1	6/2011 Marliani et al.	2013/0084257 A1	4/2013 Ishida et al.			
2011/0142945 A1	6/2011 Chen et al.	2013/0085123 A1	4/2013 Zhao et al.			
2011/0152840 A1	6/2011 Lee et al.	2013/0089574 A1	4/2013 Stock et al.			
2011/0158920 A1	6/2011 Fisher et al.	2013/0090318 A1	4/2013 Gainer et al.			
2011/0171140 A1	7/2011 Illum et al.	2013/0102781 A1	4/2013 Ely et al.			
2011/0190201 A1	8/2011 Wood, Jr. et al.	2013/0108551 A1	5/2013 Gruell et al.			
2011/0195031 A1	8/2011 Du	2013/0116215 A1	5/2013 Lleo et al.			
2011/0238003 A1	9/2011 Karabelas et al.	2013/0116222 A1	5/2013 Altomari et al.			
2011/0244043 A1	10/2011 Wang et al.	2013/0122051 A1	5/2013 Gullapalli et al.			
2011/0250256 A1	10/2011 Hyun et al.	2013/0123175 A1	5/2013 McKee et al.			
2011/0250259 A1	10/2011 Buckman	2013/0123220 A1	5/2013 Queiroz			
2011/0262373 A1	10/2011 Umbert	2013/0123351 A1	5/2013 Dewitt			
2011/0275584 A1	11/2011 Volkmann et al.	2013/0131027 A1	5/2013 Schmitz et al.			
2011/0281832 A1	11/2011 Wennogle et al.	2013/0131028 A1	5/2013 Snyder et al.			
2011/0287094 A1	11/2011 Penhasi et al.	2013/0131029 A1	5/2013 Baltussen et al.			
2011/0294738 A1	12/2011 Kulopoulos et al.	2013/0149314 A1	6/2013 Bullerdiek et al.			
2011/0300167 A1	12/2011 Covic et al.	2013/0164225 A1	6/2013 Besonov et al.			
2011/0301087 A1	12/2011 McBride et al.	2013/0164346 A1	6/2013 Son et al.			
2011/0306579 A1	12/2011 Stein	2013/0165744 A1	6/2013 Carson et al.			
2011/0318405 A1	12/2011 Erwin	2013/0178452 A1	7/2013 King			
2011/0318431 A1	12/2011 Gulati	2013/0183254 A1	7/2013 Cochran et al.			
2012/0021041 A1	1/2012 Rossi et al.	2013/0183325 A1	7/2013 Sforzini et al.			
2012/0028888 A1	2/2012 Janz et al.	2013/0189193 A1	7/2013 Besonov et al.			
2012/0028910 A1	2/2012 Takruri et al.	2013/0189196 A1	7/2013 Tamarkin et al.			
2012/0028936 A1	2/2012 Popova et al.	2013/0189230 A1	7/2013 Kooy et al.			
2012/0046264 A1	2/2012 Lieb et al.	2013/0189368 A1	7/2013 Mosqueira et al.			
2012/0046518 A1	2/2012 Yoakum et al.	2013/0210709 A1	8/2013 Covic et al.			
2012/0058171 A1	3/2012 Zeeman et al.	2013/0216550 A1	8/2013 Penninger et al.			
2012/0058962 A1	3/2012 Sparrow et al.	2013/0216596 A1	8/2013 Fernandez et al.			
2012/0058979 A1	3/2012 Auspitz et al.	2013/0224177 A1	8/2013 Kim et al.			
2012/0064135 A1	3/2012 Harms et al.	2013/0224257 A1	8/2013 Sah et al.			
2012/0065179 A1	3/2012 Andersson	2013/0224268 A1	8/2013 Jaikaria et al.			
2012/0087872 A1	4/2012 Schuz et al.	2013/0224300 A1	8/2013 Maggio			
2012/0101073 A1	4/2012 Mannion et al.	2013/0225412 A1	8/2013 Sardari Lodriche et al.			
2012/0121517 A1	5/2012 Kim et al.	2013/0225542 A1	8/2013 Frick et al.			
2012/0121692 A1	5/2012 Fang et al.	2013/0226113 A1	8/2013 Langguth et al.			
2012/0122829 A1	5/2012 Masini et al.	2013/0243696 A1	9/2013 Wang et al.			
2012/0128654 A1	5/2012 Terpstra et al.	2013/0245253 A1	9/2013 Mook et al.			
2012/0128683 A1	5/2012 Shantha	2013/0245570 A1	9/2013 Jackson			
2012/0128733 A1	5/2012 Perrin et al.	2013/0261096 A1	10/2013 Merian et al.			
		2013/0266645 A1	10/2013 Schoenecker et al.			
		2013/0267485 A1	10/2013 Da Silva			
		2013/0273167 A1	10/2013 Kim et al.			
		2013/0274211 A1	10/2013 Prusthy et al.			

US 8,993,549 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2013/0280213 A1	10/2013	Voskuhl	WO	WO2013102665 A1	7/2013	
2013/0316374 A1	11/2013	Menon et al.	WO	WO2013102665 A1	7/2013	
2013/0317065 A1	11/2013	Seto et al.	WO	WO2013106437 A1	7/2013	
2013/0317315 A1	11/2013	Tsang et al.	WO	WO2013113690	8/2013	
2013/0324565 A1	12/2013	Zhao et al.	WO	WO2013124415 A1	8/2013	
2013/0331363 A1	12/2013	Zhao et al.	WO	WO2013127727 A1	9/2013	
2013/0338124 A1	12/2013	Zhao et al.	WO	WO2013127728 A1	9/2013	
2013/0345187 A1	12/2013	Rodriguez	WO	WO2013144356 A1	10/2013	
2014/0018335 A1	1/2014	Seto et al.	WO	WO2013149258 A2	10/2013	
2014/0024590 A1	1/2014	Taylor et al.	WO	WO2013158454 A2	10/2013	
2014/0031289 A1	1/2014	Kim et al.	WO	WO2013170052 A1	11/2013	
2014/0031323 A1	1/2014	Perez	WO	WO2013178587 A1	12/2013	
2014/0066416 A1	3/2014	Leunis et al.	WO	WO2013181449 A1	12/2013	
2014/0072531 A1	3/2014	Oh et al.	WO	WO2014001904 A1	1/2014	
2014/0079686 A1	3/2014	Prouty et al.	WO	WO2014004424 A1	1/2014	
2014/0088058 A1	3/2014	Maurizio	WO	WO2014009434 A1	1/2014	
2014/0088059 A1	3/2014	Santha et al.	WO	WO2014018569 A1	1/2014	
2014/0094426 A1	4/2014	Drummond et al.	WO	WO2014018570 A1	1/2014	
2014/0100159 A1	4/2014	Conrad	WO	WO2014018571 A2	1/2014	
2014/0100206 A1	4/2014	Cacace et al.	WO	WO2014018856 A1	1/2014	
2014/0113889 A1	4/2014	Haine et al.	WO	WO2014018932 A2	1/2014	
2014/0127185 A1	5/2014	Sayeed et al.	WO	WO2014031958 A1	2/2014	
2014/0127280 A1	5/2014	Jukarainen et al.	WO	WO2014041120 A1	3/2014	
2014/0127308 A1	5/2014	Opala et al.	WO	WO2014052792 A1	4/2014	
2014/0128798 A1	5/2014	Malanchin et al.	WO	WO2014056897 A1	4/2014	
2014/0148491 A1	5/2014	Valia et al.	WO	WO2014066442 A2	5/2014	
2014/0186332 A1	7/2014	Ezrin et al.	WO	WO2014074846 A1	5/2014	
2014/0187487 A1	7/2014	Shoichet et al.	WO	WO2014076231 A1	5/2014	
2014/0193523 A1	7/2014	Henry	WO	WO2014076569 A2	5/2014	
2014/0194396 A1	7/2014	Wennogle et al.	WO	WO2014081598 A1	5/2014	
2014/0206616 A1	7/2014	Ko et al.	WO	WO2014086739 A1	6/2014	
FOREIGN PATENT DOCUMENTS						
WO	WO03028667	4/2003		OTHER PUBLICATIONS		
WO	WO2004014432	2/2004		Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.		
WO	WO2005081825	9/2005		Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.		
WO	WO2007120868	10/2007		Gattefossé Sas, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.		
WO	WO2010146872	12/2010		Gattefossé Sas, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.		
WO	WO2012055814 A1	5/2012		Gattefossé Sas, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.		
WO	WO2012055840 A1	5/2012		Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.		
WO	WO2012065740	5/2012		Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.		
WO	WO2012098090 A1	7/2012		Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.		
WO	WO2012116277 A1	8/2012		Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.		
WO	WO2012118563 A2	9/2012		Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.		
WO	WO2012120365 A1	9/2012		ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.		
WO	WO2012127501 A2	9/2012		* cited by examiner		
WO	WO2012156561 A1	11/2012				
WO	WO2012156822 A1	11/2012				
WO	WO2012156822 A2	11/2012				
WO	WO2012158483 A2	11/2012				
WO	WO2012166909 A1	12/2012				
WO	WO2012170578 A1	12/2012				
WO	WO20130111501 A1	1/2013				
WO	WO2013025449 A1	2/2013				
WO	WO2013028639 A1	2/2013				
WO	WO2013035101 A1	3/2013				
WO	WO2013044067 A1	3/2013				
WO	WO2013045404 A2	4/2013				
WO	WO2013059285 A1	4/2013				
WO	WO2013063279 A1	5/2013				
WO	WO2013064620 A1	5/2013				
WO	WO2013071281 A1	5/2013				
WO	WO2013088254	6/2013				

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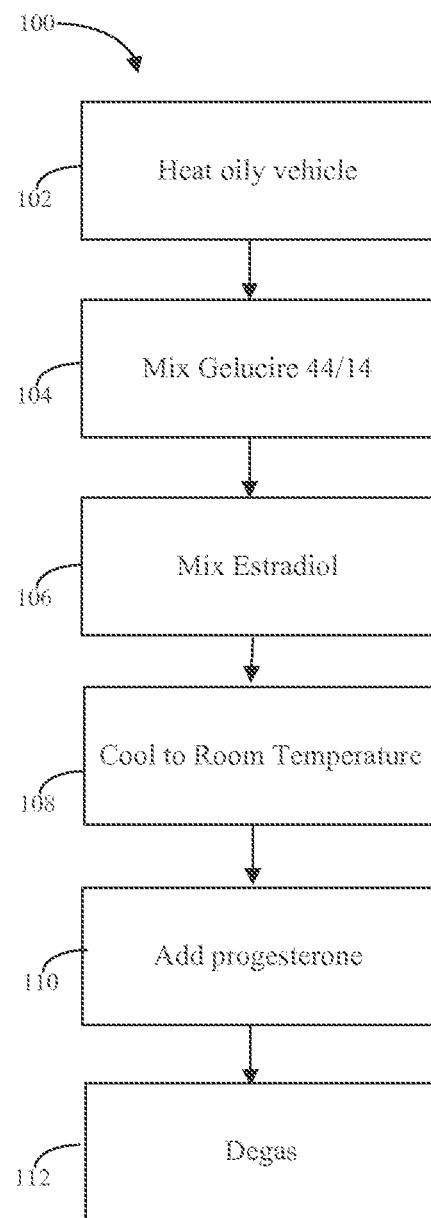
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Fig. 1

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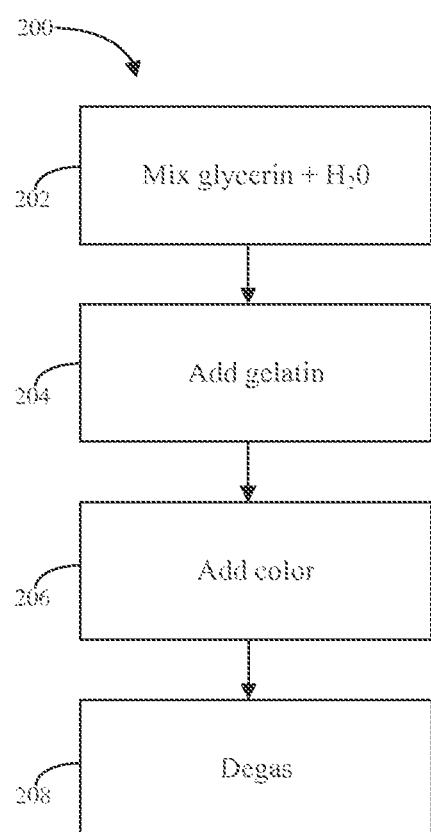


Fig. 2

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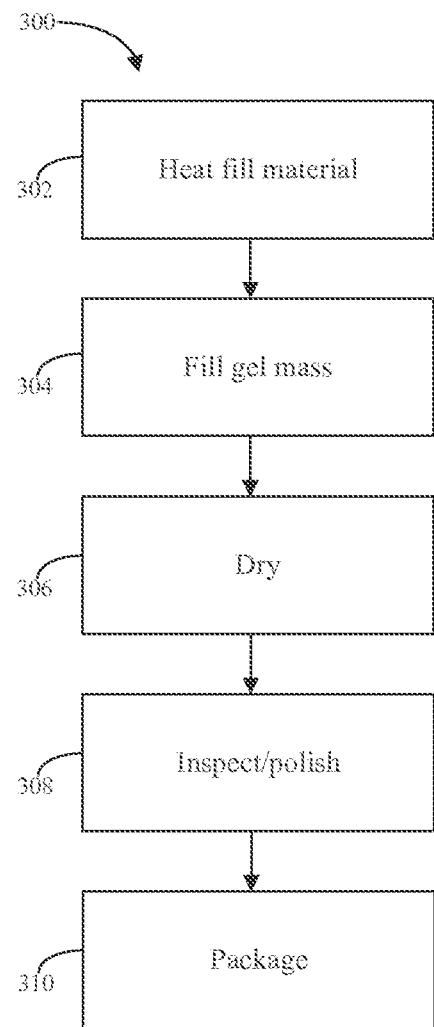


Fig. 3

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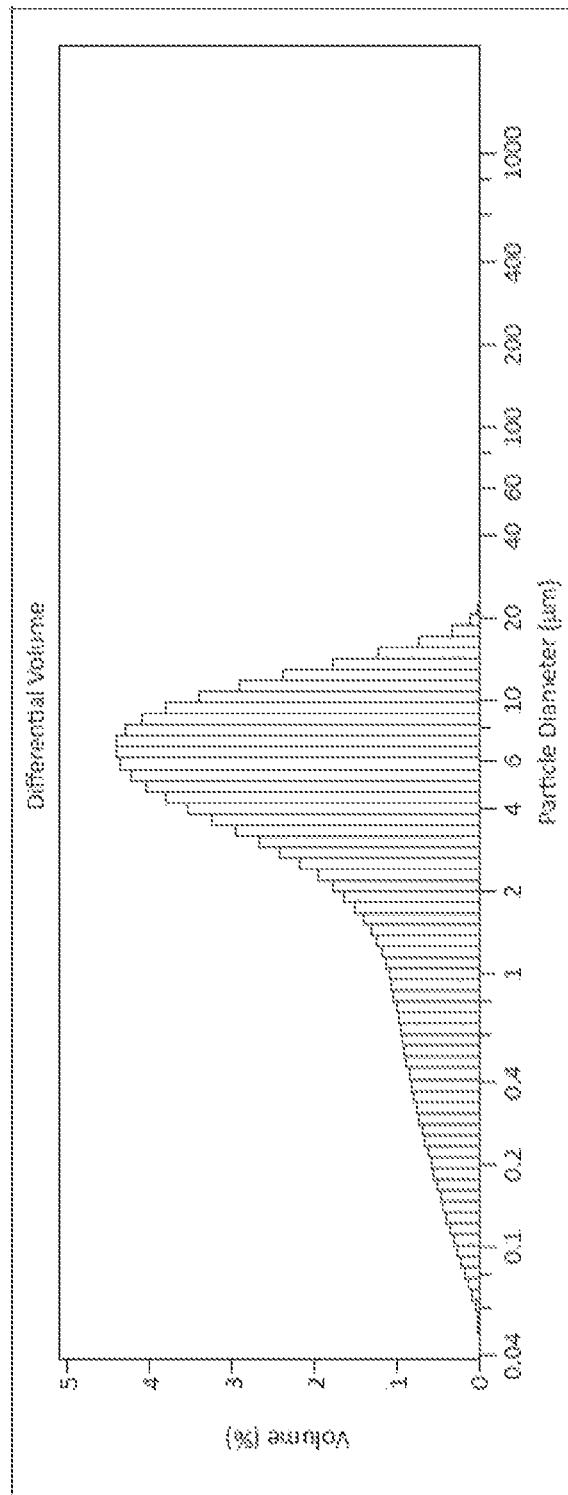


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCES TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/099,571, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which is a continuation of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken

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daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. DEFINITIONS

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, T_{max} .

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. DESCRIPTION AND PREFERRED EMBODIMENTS

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for

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use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

10 Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

15 20 Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

25 30 The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm . The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery 35 and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, 40 ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

45 50 The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 55 60 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . 60 The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

65 Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be

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combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Capmul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

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In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2, 3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days

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identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g

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solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

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TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference—Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

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Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

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Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (5:80:15)	6	Clear after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:47:47)	12	Clear after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethyl ether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg

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progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM: Gelucire 44/14 (9:1)	86.4
Capmul MCM: Gelucire 44/14 (7:3)	70.5
Capmul MCM: Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C./+/-2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

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Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglyc- erides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxy-32- glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxy1-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an X75 of 17.3 μm , and an X25 of 5.3 μm . The Beckman Device also yielded that the mean particle size is 11.8 μm , the median particle size is 11.04 μm , the mode particle size is 13.6 μm , and the standard deviation is 7.8 μm .

10 15 Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula:Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	Qty/Capsule % w/w (mg)	Amount/Batch (kg)	
1.	Progesterone, USP micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:		100.00	700.00	7.00	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

An example of the final formulation is provided in Table 40 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

45 Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and 50 partially solubilized progesterone comprising:

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

55 Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an X75 of 7.442 μm , and an X25 of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 4.

Item No.	INGREDIENT(S)	Label Claim (mg)	Qty/ Capsule % w/w (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26
3.	Capmul MCM, NF		73.371	146.74
4.	Gelucire 44/14, NF		1.500	3.00
Total:		100.000	200.00mg	2000.00

The manufacturing process is as follows. Capmul MCM is 65 heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and

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dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
	Total:	100.00	600.0	mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the

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study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel

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vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+-3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+-10° C. The wedge temperature may be 38° C.+-3° C. The drum cooling temperature may be 4° C.+-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thick-

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ness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and
wherein the solubilizing agent comprises an effective amount of a monoglyceride, a diglyceride or a combination thereof containing an ester of a C6-C12 fatty acid.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. The pharmaceutical composition of claim 1, wherein the estradiol does not precipitate for at least 14 days.

7. A pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and
wherein the solubilizing agent comprises an effective amount of a monoglyceride thereof containing an ester of a C6-C12 fatty acid.

8. The pharmaceutical composition of claim 7, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

9. The pharmaceutical composition of claim 7, wherein the composition is formulated as a gelatin capsule.

10. The pharmaceutical composition of claim 7, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

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11. The pharmaceutical composition of claim 7, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

12. The pharmaceutical composition of claim 7, wherein the estradiol does not precipitate for at least 14 days. 5

13. A pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent;

wherein each of the estradiol and the suspended progest- 10

erone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprising an effective 15 amount of a diglyceride containing an ester of a C6-C12 fatty acid.

14. The pharmaceutical composition of claim 13, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solu- 20 bilizing agent.

15. The pharmaceutical composition of claim 13, wherein the composition is formulated in a gelatin capsule.

16. The pharmaceutical composition of claim 13, wherein the estradiol has a dosage strength of at least about 0.125 mg 25 and wherein the progesterone has a dosage strength of at least about 25 mg.

17. The pharmaceutical composition of claim 13, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1. 30

18. The pharmaceutical composition of claim 13, wherein the estradiol does not precipitate for at least 14 days.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,993,549 B2
APPLICATION NO. : 14/475864
DATED : March 31, 2015
INVENTOR(S) : Brian A. Bernick et al.

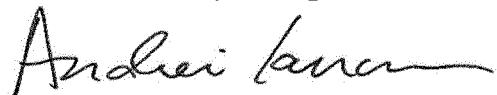
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Second Day of April, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,993,549 B2
APPLICATION NO. : 14/475864
DATED : March 31, 2015
INVENTOR(S) : Brian A. Bernick et al.

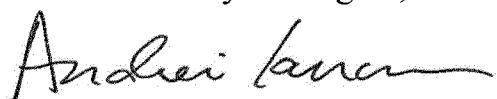
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 20, Claim 7, Line 56: Delete "thereof".

Signed and Sealed this
Thirteenth Day of August, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT G



US009006222B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 9,006,222 B2
(45) **Date of Patent:** *Apr. 14, 2015

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 13/843,428, filed on Mar. 15, 2013, which is a continuation-in-part of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178.

(60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012.

(51) **Int. Cl.**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Grant et al.
3,198,707 A	8/1965	Nomaine et al.
3,478,070 A	11/1969	Smith et al.

3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Higuchi et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes
4,012,496 A	3/1977	Hartmann
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	Van Der Vies
4,093,709 A	6/1978	Choi
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong
4,237,885 A	12/1980	Wong
4,310,510 A	1/1982	Sherman et al.
4,327,725 A	5/1982	Cortese et al.
4,372,951 A	2/1983	Vorys
4,384,096 A	5/1983	Sonnabend
4,393,871 A	7/1983	Vorhauer

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI 1001367-9 A2	7/2012
CN	102258455 A	11/2011

(Continued)

OTHER PUBLICATIONS

PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.
US 6,214,374, Apr. 10, 2001, Schmirler, et al. (withdrawn).
Acog, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, Acog, No. 141, vol. 123, No. 1, Jan. 2014, *Obstetrics & Gynecology*.

Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.

Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.

(Continued)

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(57)

ABSTRACT

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

US 9,006,222 B2

Page 2

(56)	References Cited				
U.S. PATENT DOCUMENTS					
4,402,695 A	9/1983 Wong	5,709,844 A	1/1998 Arbeit et al.		
4,423,151 A	12/1983 Baranczuk	5,719,197 A	2/1998 Kanios et al.		
4,449,980 A	5/1984 Millar et al.	5,735,801 A	4/1998 Caillouette		
4,610,687 A	9/1986 Fogwell	5,739,176 A	4/1998 Dunn et al.		
4,629,449 A	12/1986 Wong	5,744,463 A	4/1998 Bair		
4,732,763 A	3/1988 Beck et al.	5,747,058 A	5/1998 Tipton et al.		
4,738,957 A	4/1988 Laurent et al.	5,762,614 A	6/1998 Caillouette		
4,756,907 A	7/1988 Beck et al.	5,770,176 A	6/1998 Nargessi		
4,762,717 A	8/1988 Crowley	5,770,219 A	6/1998 Chiang et al.		
4,788,062 A	11/1988 Gale et al.	5,770,220 A	6/1998 Meconi et al.		
4,816,257 A	3/1989 Buster et al.	5,770,227 A	6/1998 Dong et al.		
4,822,616 A	4/1989 Zimmermann et al.	5,776,495 A	7/1998 Duclos et al.		
4,865,848 A	9/1989 Cheng et al.	5,780,044 A	7/1998 Yewey et al.		
4,900,734 A	2/1990 Maxson et al.	5,780,050 A	7/1998 Jain et al.		
4,906,475 A	3/1990 Kim	5,788,980 A	8/1998 Nabahi		
4,942,158 A	7/1990 Sarpotdar et al.	5,788,984 A	8/1998 Guenther et al.		
4,961,931 A	10/1990 Wong	5,789,442 A	8/1998 Garfield et al.		
5,030,629 A	7/1991 Rajadhyaksha	5,811,416 A	9/1998 Chwalisz et al.		
5,064,654 A	11/1991 Berner et al.	5,811,547 A	9/1998 Nakamichi et al.		
5,108,995 A	4/1992 Casper	5,814,329 A	9/1998 Shah		
5,128,138 A	7/1992 Blank	5,820,878 A	10/1998 Hirano et al.		
5,130,137 A	7/1992 Crowley	5,827,200 A	10/1998 Caillouette		
5,140,021 A	8/1992 Maxson et al.	5,840,327 A	11/1998 Gale et al.		
5,211,952 A	5/1993 Pike et al.	5,843,468 A	12/1998 Burkoth et al.		
5,252,334 A	10/1993 Chiang et al.	5,843,979 A	12/1998 Wille et al.		
5,280,023 A	1/1994 Ehrlich et al.	5,858,394 A	1/1999 Lipp et al.		
5,288,496 A	2/1994 Lewis	5,863,552 A	1/1999 Yue		
5,340,584 A	8/1994 Spicer et al.	5,866,603 A	2/1999 Li et al.		
5,340,585 A	8/1994 Pike et al.	5,882,676 A	3/1999 Lee et al.		
5,340,586 A	8/1994 Pike et al.	5,885,612 A	3/1999 Meconi et al.		
5,362,497 A	11/1994 Yamada et al.	5,888,533 A	3/1999 Dunn		
5,382,573 A	1/1995 Casper	5,891,462 A	4/1999 Carrara		
5,393,528 A	2/1995 Staab	5,891,868 A	4/1999 Cummings et al.		
5,393,529 A	2/1995 Hoffmann et al.	5,898,038 A	4/1999 Yallampalli et al.		
5,419,910 A	5/1995 Lewis	5,902,603 A	5/1999 Chen et al.		
5,468,736 A	11/1995 Hodgen	5,904,931 A	5/1999 Lipp et al.		
5,474,783 A	12/1995 Miranda et al.	5,906,830 A	5/1999 Farinas et al.		
5,480,776 A	1/1996 Dullien	5,912,010 A	6/1999 Wille et al.		
5,514,673 A	5/1996 Heckenmuller et al.	5,916,176 A	6/1999 Caillouette		
5,516,528 A	5/1996 Hughes et al.	RE36,247 E	7/1999 Plunkett et al.		
5,527,534 A	6/1996 Myhling	5,919,477 A	7/1999 Bevan et al.		
5,529,782 A	6/1996 Staab	5,922,349 A	7/1999 Elliesen et al.		
5,538,736 A	7/1996 Hoffmann et al.	5,928,666 A	7/1999 Farinas et al.		
5,543,150 A	8/1996 Bologna et al.	5,942,243 A	8/1999 Shah		
5,547,948 A	8/1996 Barcomb	5,952,000 A	9/1999 Venkateshwaran et al.		
5,556,635 A	9/1996 Istin et al.	5,958,446 A	9/1999 Miranda et al.		
5,565,199 A	10/1996 Page et al.	5,962,445 A	10/1999 Stewart		
5,567,831 A	10/1996 Li	5,968,919 A	10/1999 Samour et al.		
5,569,652 A	10/1996 Beier et al.	5,972,372 A	10/1999 Saleh et al.		
5,580,572 A	12/1996 Mikler et al.	5,985,311 A	11/1999 Cordes et al.		
5,582,592 A	12/1996 Kendrick	5,985,850 A	11/1999 Falk et al.		
5,585,370 A	12/1996 Casper	5,985,861 A	11/1999 Levine et al.		
5,595,759 A	1/1997 Wright et al.	5,989,568 A	11/1999 Breton et al.		
5,595,970 A	1/1997 Garfield et al.	5,993,856 A	11/1999 Ragavan et al.		
5,605,702 A	2/1997 Teillaud et al.	6,001,846 A	12/1999 Edwards et al.		
5,607,691 A	3/1997 Hale et al.	6,007,835 A	12/1999 Bon Lapillonne et al.		
5,607,693 A	3/1997 Bonte et al.	6,010,715 A	1/2000 Wick et al.		
5,609,617 A	3/1997 Shealy et al.	6,013,276 A	1/2000 Math et al.		
5,620,705 A	4/1997 Dong et al.	6,022,562 A	2/2000 Autant et al.		
5,626,866 A	5/1997 Ebert et al.	6,024,974 A	2/2000 Li		
5,629,021 A	5/1997 Wright	6,024,976 A	2/2000 Miranda et al.		
5,633,011 A	5/1997 Dong et al.	6,028,057 A	2/2000 Burns		
5,633,242 A	5/1997 Oettel et al.	6,030,948 A	2/2000 Mann		
5,639,743 A	6/1997 Kaswan et al.	6,039,968 A	3/2000 Nabahi		
5,653,983 A	8/1997 Meybeck et al.	6,040,340 A	3/2000 Chwalisz et al.		
5,656,286 A	8/1997 Miranda et al.	6,056,972 A	5/2000 Hermsmeyer		
5,660,839 A	8/1997 Allec et al.	6,060,077 A	5/2000 Meignant		
5,662,927 A	9/1997 Ehrlich et al.	6,068,853 A	5/2000 Giannos et al.		
5,663,160 A	9/1997 Meybeck et al.	6,074,625 A	6/2000 Hawthorne et al.		
5,676,968 A	10/1997 Lipp et al.	6,077,531 A	6/2000 Salin-Drouin		
5,677,292 A	10/1997 Li et al.	6,080,118 A	6/2000 Blythe		
5,686,097 A	11/1997 Taskovich et al.	6,083,178 A	7/2000 Caillouette		
5,693,335 A	12/1997 Xia et al.	6,086,916 A	7/2000 Agnus et al.		
5,694,947 A	12/1997 Lehtinen et al.	6,087,352 A	7/2000 Trout		
5,700,480 A	12/1997 Hille et al.	6,090,404 A	7/2000 Meconi et al.		
		6,096,338 A	8/2000 Lacy et al.		
		6,106,848 A	8/2000 Preuylh et al.		
		6,117,446 A	9/2000 Place		
		6,117,450 A	9/2000 Dittgen et al.		

US 9,006,222 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

6,124,362 A	9/2000	Bradbury et al.	6,537,580 B1	3/2003	Savoir et al.
6,133,251 A	10/2000	Dittgen et al.	6,538,039 B2	3/2003	Laurent
6,133,320 A	10/2000	Yallampalli et al.	6,544,196 B2	4/2003	Caillouette
6,139,868 A	10/2000	Hoffmann	6,544,553 B1	4/2003	Hsia et al.
6,139,873 A	10/2000	Hughes, Jr. et al.	6,548,053 B1	4/2003	Stewart et al.
6,149,935 A	11/2000	Chiang et al.	6,548,491 B2	4/2003	Tanabe et al.
6,153,216 A	11/2000	Cordes et al.	6,551,611 B2	4/2003	Elliesen et al.
6,165,491 A	12/2000	Grasset et al.	6,555,131 B1	4/2003	Wolff et al.
6,165,975 A	12/2000	Adams et al.	6,562,367 B1	5/2003	Wolff et al.
6,187,323 B1	2/2001	Aiache et al.	6,562,370 B2	5/2003	Luo et al.
6,187,339 B1	2/2001	de Haan et al.	6,562,790 B2	5/2003	Chein
6,190,331 B1	2/2001	Caillouette	6,569,463 B2	5/2003	Patel et al.
6,201,072 B1	3/2001	Rathi et al.	6,583,129 B1	6/2003	Mazer et al.
6,217,886 B1	4/2001	Onyuksel et al.	6,586,006 B2	7/2003	Roser et al.
6,225,297 B1	5/2001	Stockemann et al.	6,589,549 B2	7/2003	Shih et al.
6,227,202 B1	5/2001	Matapurkar	6,593,317 B1	7/2003	De Ziegler et al.
6,228,383 B1	5/2001	Hansen et al.	6,599,519 B1	7/2003	Seo et al.
6,228,852 B1	5/2001	Shaak	6,610,670 B2	8/2003	Backensfeld et al.
6,242,509 B1	6/2001	Berger et al.	6,610,674 B1	8/2003	Schreiber
6,245,811 B1	6/2001	Horrobin et al.	6,610,652 B2	10/2003	Savoir et al.
6,262,115 B1	7/2001	Guittard et al.	6,635,274 B1	10/2003	Masiz et al.
6,267,984 B1	7/2001	Beste et al.	6,638,528 B1	10/2003	Kanios
6,274,165 B1	8/2001	Meconi et al.	6,638,536 B2	10/2003	Savoir et al.
6,277,418 B1	8/2001	Markaverich et al.	6,645,528 B1	11/2003	Straub et al.
6,283,927 B1	9/2001	Caillouette	6,649,155 B1	11/2003	Dunlop et al.
6,287,588 B1	9/2001	Shih et al.	6,653,298 B2	11/2003	Potter et al.
6,287,693 B1	9/2001	Savoir et al.	6,656,929 B1	12/2003	Agnus et al.
6,294,188 B1	9/2001	Ragavan et al.	6,660,726 B2	12/2003	Hill et al.
6,294,192 B1	9/2001	Patel et al.	6,663,608 B2	12/2003	Rathbone et al.
6,294,550 B1	9/2001	Place et al.	6,663,895 B2	12/2003	Savoir et al.
6,299,900 B1	10/2001	Reed et al.	6,682,757 B1	1/2004	Wright
6,303,132 B1	10/2001	Nelson	6,692,763 B1	2/2004	Cummings et al.
6,303,588 B1	10/2001	Danielov	6,708,822 B1	3/2004	Muni
6,306,841 B1	10/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.
6,306,914 B1	10/2001	Ziegler et al.	6,720,333 B2	5/2004	Beckett et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,737,081 B2	6/2004	Griffin et al.
6,309,848 B1	10/2001	Howett et al.	6,743,448 B2	6/2004	Kryger
6,312,703 B1	11/2001	Orthoefer	6,743,815 B2	6/2004	Huebner et al.
6,328,987 B1	12/2001	Marini	6,747,018 B2	6/2004	Tanabe et al.
6,342,491 B1	1/2002	Dey et al.	6,750,291 B2	6/2004	Kim et al.
6,344,211 B1	2/2002	Hille	6,756,208 B2	6/2004	Griffin et al.
6,372,209 B1	4/2002	Chrisope	6,776,164 B2	8/2004	Bunt et al.
6,372,245 B1	4/2002	Bowman et al.	6,787,152 B2	9/2004	Kirby et al.
6,372,246 B1	4/2002	Wei	6,805,877 B2	10/2004	Massara et al.
6,387,390 B1	5/2002	Deaver et al.	6,809,085 B1	10/2004	Elson et al.
6,402,705 B1	6/2002	Caillouette	6,818,226 B2	10/2004	Elson et al.
6,416,778 B1	7/2002	Ragavan et al.	6,821,524 B2	11/2004	Marini
6,420,352 B1	7/2002	Knowles	6,841,716 B1	1/2005	Tsutsumi
6,423,039 B1	7/2002	Rathbone et al.	6,844,334 B2	1/2005	Hill et al.
6,423,683 B1	7/2002	Heaton et al.	6,855,703 B1	2/2005	Hill et al.
6,432,438 B1	8/2002	Shukla	6,860,859 B2	3/2005	Mehrotra et al.
6,436,633 B1	8/2002	Kreider et al.	6,866,865 B2	3/2005	Hsia et al.
6,440,454 B1	8/2002	Santoro et al.	6,869,969 B2	3/2005	Huebner et al.
6,444,224 B1	9/2002	Rathbone et al.	6,878,518 B2	4/2005	Whitehead
6,444,234 B1	9/2002	Kirby et al.	6,901,278 B1	5/2005	Notelovitz
6,451,300 B1	9/2002	Dunlop et al.	6,905,705 B2	6/2005	Palm et al.
6,451,339 B2	9/2002	Patel et al.	6,911,211 B2	6/2005	Eini et al.
6,451,779 B1	9/2002	Hesch	6,919,438 B2	6/2005	Wright
6,455,246 B1	9/2002	Howett et al.	6,923,988 B2	8/2005	Patel et al.
6,455,517 B1	9/2002	Tanabe et al.	6,924,274 B2	8/2005	Lardy et al.
6,465,004 B1	10/2002	Rossi Montero et al.	6,932,983 B1	8/2005	Straub et al.
6,465,005 B1	10/2002	Biali et al.	6,939,558 B2	9/2005	Massara et al.
6,465,006 B1	10/2002	Zhang et al.	6,943,021 B2	9/2005	Klausner et al.
6,468,526 B2	10/2002	Chrisope	6,958,327 B1	10/2005	Hillisch et al.
6,469,016 B1	10/2002	Place et al.	6,960,337 B2	11/2005	Daniels et al.
6,472,434 B1	10/2002	Place et al.	6,962,691 B1	11/2005	Lulla et al.
6,479,232 B1	11/2002	Howett et al.	6,962,908 B2	11/2005	Aloba et al.
6,495,160 B2	12/2002	Esposito et al.	6,967,194 B1	11/2005	Matsuo et al.
6,500,814 B1	12/2002	Hesch	6,974,569 B2	12/2005	Dunlop et al.
6,503,896 B1	1/2003	Tanabe et al.	6,977,250 B2	12/2005	Rodriguez
6,511,969 B1	1/2003	Hermsmeyer	6,978,945 B2	12/2005	Wong et al.
6,521,250 B2	2/2003	Meconi et al.	6,995,149 B1	2/2006	Endrikat et al.
6,526,980 B1	3/2003	Tracy et al.	7,004,321 B1	2/2006	Palm et al.
6,528,094 B1	3/2003	Savoir et al.	7,005,429 B2	2/2006	Dey et al.
6,531,149 B1	3/2003	Kirstgen et al.	7,011,846 B2	3/2006	Shojaei et al.
			7,018,992 B2	3/2006	Koch et al.
			7,030,104 B2	4/2006	Gray et al.
			7,030,157 B2	4/2006	Ke et al.
			RE39,104 E	5/2006	Duclos et al.

US 9,006,222 B2

Page 4

(56)	References Cited				
U.S. PATENT DOCUMENTS					
7,074,779 B2	7/2006	Sui et al.	7,939,104 B2	5/2011	Barbera et al.
7,083,590 B1	8/2006	Bunt et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,091,213 B2	8/2006	Metcalf, III et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
7,094,228 B2	8/2006	Zhang et al.	7,960,368 B2	6/2011	Nickisch et al.
7,097,853 B1	8/2006	Garbe et al.	7,989,436 B2	8/2011	Hill et al.
7,101,342 B1	9/2006	Caillouette	7,989,487 B2	8/2011	Welsh et al.
7,105,573 B2	9/2006	Krajcik et al.	8,022,053 B2	9/2011	Mueller et al.
7,135,190 B2	11/2006	Piao et al.	8,048,017 B2	11/2011	Xu
7,153,522 B1	12/2006	Ikeura et al.	8,048,869 B2	11/2011	Bunschoten et al.
7,163,681 B2	1/2007	Giles-Komar	8,063,030 B2	11/2011	Ellman
7,163,699 B2	1/2007	Besse	8,071,576 B2	12/2011	Coelingh Bennink et al.
7,175,850 B2	2/2007	Cevc	8,071,729 B2	12/2011	Giles-Komar et al.
7,179,799 B2	2/2007	Hill et al.	8,075,916 B2	12/2011	Song et al.
7,196,074 B2	3/2007	Blye et al.	8,075,917 B2	12/2011	Chung et al.
7,198,800 B1	4/2007	Ko	8,076,317 B2	12/2011	Kulmann
7,198,801 B2	4/2007	Carrara et al.	8,076,319 B2	12/2011	Leonard
7,226,910 B2	6/2007	Wilson et al.	8,080,553 B2	12/2011	Keith et al.
7,247,625 B2	7/2007	Zhang et al.	8,088,605 B2	1/2012	Beaudet et al.
7,250,446 B2	7/2007	Sangita et al.	8,096,940 B2	1/2012	Josephson et al.
7,267,829 B2	9/2007	Kirby et al.	8,101,209 B2	1/2012	Legrand et al.
7,300,926 B2	11/2007	Prokai et al.	8,101,773 B2	1/2012	Smith
7,303,763 B2	12/2007	Ho	8,114,152 B2	2/2012	Furst
7,317,037 B2	1/2008	Fensome et al.	8,114,434 B2	2/2012	Sasaki et al.
7,329,654 B2	2/2008	Kanojia et al.	8,114,442 B2	2/2012	Tucker et al.
7,335,650 B2	2/2008	Potter et al.	8,119,741 B2	2/2012	Pavlin
7,374,779 B2	5/2008	Chen et al.	8,124,118 B2	2/2012	Lennernaes et al.
7,378,404 B2	5/2008	Peters	8,124,595 B2	2/2012	Boissonneault
7,381,427 B2	6/2008	Ancira et al.	8,147,561 B2	4/2012	Binmoeller
7,387,789 B2	6/2008	Klose et al.	8,148,546 B2	4/2012	Schuster et al.
7,388,006 B2	6/2008	Schmees et al.	8,158,613 B2	4/2012	Stanforth et al.
7,414,043 B2	8/2008	Kosemund et al.	8,158,614 B2	4/2012	Lambert et al.
7,427,413 B2	9/2008	Savoir et al.	8,163,722 B2	4/2012	Savoir et al.
7,427,609 B2	9/2008	Leonard	8,177,449 B2	5/2012	Bayly et al.
7,429,576 B2	9/2008	Labrie	8,182,833 B2	5/2012	Hermsmeyer
7,431,941 B2	10/2008	Besins et al.	8,187,615 B2	5/2012	Friedman
7,456,159 B2	11/2008	Houze et al.	8,195,403 B2	6/2012	Ishikawa et al.
7,459,445 B2	12/2008	Hill et al.	8,202,736 B2	6/2012	Mousa et al.
7,465,587 B2	12/2008	Imrich	8,217,024 B2	7/2012	Ahmed et al.
7,470,433 B2	12/2008	Carrara et al.	8,221,785 B2	7/2012	Chien
7,485,666 B2	2/2009	Villanueva et al.	8,222,008 B2	7/2012	Thoene
7,497,855 B2	3/2009	Ausiello et al.	8,222,237 B2	7/2012	Nickisch et al.
7,498,303 B2	3/2009	Arnold et al.	8,227,454 B2	7/2012	Hill et al.
7,534,765 B2	5/2009	Gregg et al.	8,227,509 B2	7/2012	Castro et al.
7,534,780 B2	5/2009	Wyrwa et al.	8,241,664 B2	8/2012	Dudley et al.
7,550,142 B2	6/2009	Giles-Komar et al.	8,247,393 B2	8/2012	Ahmed et al.
7,563,565 B1	7/2009	Matsuo et al.	8,257,724 B2	9/2012	Cromack et al.
7,569,274 B2	8/2009	Besse et al.	8,257,725 B2	9/2012	Cromack et al.
7,572,779 B2	8/2009	Aloba et al.	8,268,352 B2	9/2012	Vaya et al.
7,572,780 B2	8/2009	Hermsmeyer	8,268,806 B2	9/2012	Labrie
7,589,082 B2	9/2009	Savoir et al.	8,268,878 B2	9/2012	Armer et al.
7,671,027 B2	3/2010	Loumaye	8,273,730 B2	9/2012	Fernandez et al.
7,674,783 B2	3/2010	Hermsmeyer	8,287,888 B2	10/2012	Song et al.
7,687,281 B2	3/2010	Roth et al.	8,288,366 B2	10/2012	Chochinov et al.
7,687,485 B2	3/2010	Levinson et al.	8,318,898 B2	11/2012	Fasel et al.
7,694,683 B2	4/2010	Callister et al.	8,324,193 B2	12/2012	Lee Sepsick et al.
7,704,983 B1	4/2010	Hodgen et al.	8,329,680 B2	12/2012	Evans et al.
7,727,720 B2	6/2010	Dhallan	8,337,814 B2	12/2012	Osbakken et al.
7,732,408 B2	6/2010	Josephson et al.	8,344,007 B2	1/2013	Tang et al.
7,749,989 B2	7/2010	Hill et al.	8,349,820 B2	1/2013	Zeun et al.
7,767,656 B2	8/2010	Shoichet et al.	8,353,863 B2	1/2013	Imran
7,799,769 B2	9/2010	White et al.	8,357,723 B2	1/2013	Satyam
7,815,936 B2	10/2010	Hasenzahl et al.	8,361,995 B2	1/2013	Schramm
7,815,949 B2	10/2010	Cohen	8,362,091 B2	1/2013	Tamarkin et al.
7,829,115 B2	11/2010	Besins et al.	8,372,424 B2	2/2013	Berry et al.
7,829,116 B2	11/2010	Griswold et al.	8,372,806 B2	2/2013	Boehler et al.
RE42,012 E	12/2010	Deaver et al.	8,377,482 B2	2/2013	Laurie et al.
7,850,992 B2	12/2010	Kim et al.	8,377,994 B2	2/2013	Gray et al.
7,854,753 B2	12/2010	Kraft et al.	8,394,759 B2	3/2013	Barathur et al.
7,858,607 B2	12/2010	Mamchur	8,415,332 B2	4/2013	Diliberti et al.
RE42,072 E	1/2011	Deaver et al.	8,420,111 B2	4/2013	Hermsmeyer
7,862,552 B2	1/2011	McIntyre et al.	8,435,561 B2	5/2013	Besins et al.
7,867,990 B2	1/2011	Schultz et al.	8,435,972 B2	5/2013	Stein et al.
7,871,643 B2	1/2011	Lizio et al.	8,449,879 B2	5/2013	Laurent Applegate et al.
7,879,830 B2	2/2011	Wiley	8,450,108 B2	5/2013	Boyce
7,884,093 B2	2/2011	Creasy et al.	8,454,945 B2	6/2013	McCook et al.
			8,455,468 B2	6/2013	Hoffman et al.
			8,461,138 B2	6/2013	Boissonneault
			8,476,252 B2	7/2013	Achleitner et al.
			8,481,488 B2	7/2013	Carter

US 9,006,222 B2

Page 5

(56)

References Cited**U.S. PATENT DOCUMENTS**

8,486,374 B2	7/2013	Tamarkin et al.	2003/0003139 A1	1/2003	Lipp et al.
8,486,442 B2	7/2013	Matsushita et al.	2003/0004145 A1	1/2003	Leonard
8,492,368 B2	7/2013	Vanlandingham et al.	2003/0007994 A1	1/2003	Bunt et al.
8,507,467 B2	8/2013	Matsui et al.	2003/0027772 A1	2/2003	Bretton
8,512,693 B2	8/2013	Capito et al.	2003/0044453 A1	3/2003	Dittgen et al.
8,512,754 B2	8/2013	Needham	2003/0049307 A1	3/2003	Gyurik
8,518,376 B2	8/2013	Tamarkin et al.	2003/0064097 A1	4/2003	Patel et al.
8,536,159 B2	9/2013	Li et al.	2003/0072760 A1	4/2003	Sirbasku
8,540,967 B2	9/2013	Barrett et al.	2003/0091620 A1	5/2003	Fikstad et al.
8,541,400 B2	9/2013	Johnsson et al.	2003/0091640 A1	5/2003	Ramanathan et al.
8,551,462 B2	10/2013	Goldstein et al.	2003/0092691 A1	5/2003	Besse et al.
8,557,281 B2	10/2013	Halliday et al.	2003/0096012 A1	5/2003	Besse et al.
8,568,374 B2	10/2013	De Graaff et al.	2003/0104048 A1	6/2003	Patel et al.
8,591,951 B2	11/2013	Kohn et al.	2003/0109507 A1	6/2003	Frank et al.
8,613,951 B2	12/2013	Zale et al.	2003/0113268 A1	6/2003	Buenafae et al.
8,633,178 B2	1/2014	Bernick et al.	2003/0114420 A1	6/2003	Salvati et al.
8,633,180 B2	1/2014	Li et al.	2003/0114430 A1	6/2003	MacLeod et al.
8,636,787 B2	1/2014	Sabaria	2003/0124182 A1	7/2003	Shojaei et al.
8,636,982 B2	1/2014	Tamarkin et al.	2003/0124191 A1	7/2003	Besse et al.
8,653,129 B2	2/2014	Fein et al.	2003/0130558 A1	7/2003	Massara et al.
8,658,627 B2	2/2014	Voskuhl	2003/0144258 A1	7/2003	Heil et al.
8,658,628 B2	2/2014	Baucom	2003/0157157 A1	8/2003	Luo et al.
8,663,681 B2	3/2014	Ahmed et al.	2003/0166509 A1	9/2003	Edwards et al.
8,663,692 B1	3/2014	Mueller et al.	2003/0170295 A1	9/2003	Kim et al.
8,663,703 B2	3/2014	Lerner et al.	2003/0175329 A1	9/2003	Azarnoff et al.
8,664,207 B2	3/2014	Li et al.	2003/0175333 A1	9/2003	Shefer et al.
8,669,293 B2	3/2014	Levy et al.	2003/0180352 A1	9/2003	Patel et al.
8,679,552 B2	3/2014	Guthery	2003/0181353 A1	9/2003	Nyce
8,697,127 B2	4/2014	Sah	2003/0181728 A1	9/2003	Salvati et al.
8,697,710 B2	4/2014	Li et al.	2003/0191096 A1	10/2003	Leonard et al.
8,703,105 B2	4/2014	Tamarkin et al.	2003/0195177 A1	10/2003	Leonard et al.
8,709,385 B2	4/2014	Tamarkin et al.	2003/0215496 A1	11/2003	Patel et al.
8,709,451 B2	4/2014	Nam et al.	2003/0219402 A1	11/2003	Rutter
8,715,735 B2	5/2014	Funke et al.	2003/0220297 A1	11/2003	Berstein et al.
8,721,331 B2	5/2014	Raghuprasad	2003/0224057 A1	12/2003	Martin-Letellier et al.
8,722,021 B2	5/2014	Friedman et al.	2003/0224059 A1	12/2003	Lerner et al.
8,734,846 B2	5/2014	Ali et al.	2003/0225047 A1	12/2003	Caubel et al.
8,735,381 B2	5/2014	Podolski	2003/0225048 A1	12/2003	Caubel et al.
8,741,336 B2	6/2014	Dipierro et al.	2003/0225050 A1	12/2003	Grawe et al.
8,741,373 B2	6/2014	Bromley et al.	2003/0228686 A1	12/2003	Klausner et al.
8,753,661 B2	6/2014	Steimmueller et al.	2003/0229057 A1	12/2003	Caubel et al.
8,784,882 B2	7/2014	Mattern	2003/0235596 A1	12/2003	Gao et al.
2001/0005728 A1	6/2001	Guittard et al.	2003/0236236 A1	12/2003	Chen et al.
2001/0009673 A1	7/2001	Lipp et al.	2004/0009960 A1	1/2004	Heil et al.
2001/0021816 A1	9/2001	Caillouette	2004/0022820 A1	2/2004	Anderson
2001/0023261 A1	9/2001	Ryoo et al.	2004/0034001 A1	2/2004	Karara
2001/0027189 A1	10/2001	Bennink et al.	2004/0037881 A1	2/2004	Guittard et al.
2001/0029357 A1	10/2001	Bunt et al.	2004/0039356 A1	2/2004	Maki et al.
2001/0031747 A1	10/2001	DeZiegler et al.	2004/0043043 A1	3/2004	Schlyter et al.
2001/0034340 A1	10/2001	Pickar	2004/0043943 A1	3/2004	Guittard et al.
2001/0053383 A1	12/2001	Miranda et al.	2004/0044080 A1	3/2004	Place et al.
2001/0056068 A1	12/2001	Chwalisz et al.	2004/0048900 A1	3/2004	Flood
2002/0012710 A1	1/2002	Lansky	2004/0052824 A1	3/2004	Chacra-Vernet et al.
2002/0026158 A1	2/2002	Rathbone et al.	2004/0073024 A1	4/2004	Metcalf, III et al.
2002/0028788 A1	3/2002	Bunt et al.	2004/0077605 A1	4/2004	Salvati et al.
2002/0035070 A1	3/2002	Gardlik et al.	2004/0077606 A1	4/2004	Salvati et al.
2002/0058648 A1	5/2002	Hammerly	2004/0087548 A1	5/2004	Salvati et al.
2002/0058926 A1	5/2002	Rathbone et al.	2004/0087564 A1	5/2004	Wright et al.
2002/0076441 A1	6/2002	Shih et al.	2004/0089308 A1	5/2004	Welch
2002/0102308 A1	8/2002	Wei et al.	2004/0092494 A9	5/2004	Dudley
2002/0107230 A1	8/2002	Waldon et al.	2004/0092583 A1	5/2004	Shanahan-Prendergast
2002/0114803 A1	8/2002	Deaver et al.	2004/0097468 A1	5/2004	Wimalawansa
2002/0119174 A1	8/2002	Gardlik et al.	2004/0101557 A1	5/2004	Gibson et al.
2002/0119198 A1	8/2002	Gao et al.	2004/0106542 A1	6/2004	Deaver et al.
2002/0132801 A1	9/2002	Heil et al.	2004/0110732 A1	6/2004	Masini-Eteve et al.
2002/0137749 A1	9/2002	Levinson et al.	2004/0131670 A1	7/2004	Gao
2002/0142017 A1	10/2002	Simonnet	2004/0138103 A1	7/2004	Patt
2002/0151530 A1	10/2002	Leonard et al.	2004/0142012 A1	7/2004	Bunt et al.
2002/0156394 A1	10/2002	Mehrotra et al.	2004/0146539 A1	7/2004	Gupta
2002/0169150 A1	11/2002	Pickar	2004/0146894 A1	7/2004	Warrington et al.
2002/0169205 A1	11/2002	Chwalisz et al.	2004/0161435 A1	8/2004	Gupta
2002/0173510 A1	11/2002	Levinson et al.	2004/0176324 A1	9/2004	Salvati et al.
2002/0193356 A1	12/2002	Van Beek et al.	2004/0176336 A1	9/2004	Rodriguez
2002/0193758 A1	12/2002	Sandberg	2004/0185104 A1	9/2004	Piao et al.
2002/0197286 A1	12/2002	Brandman et al.	2004/0191207 A1	9/2004	Lipari et al.

US 9,006,222 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2004/0191276 A1	9/2004	Muni	2006/0089337 A1	4/2006	Casper et al.
2004/0198706 A1	10/2004	Carrara	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0210280 A1	10/2004	Liedtke	2006/0100180 A1	5/2006	Nubbemeyer et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0106004 A1	5/2006	Brody et al.
2004/0219124 A1	11/2004	Gupta	2006/0110415 A1	5/2006	Gupta
2004/0225140 A1	11/2004	Fernandez et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0234606 A1	11/2004	Levine et al.	2006/0121102 A1	6/2006	Chiang
2004/0241219 A1	12/2004	Hille et al.	2006/0121626 A1	6/2006	Imrich
2004/0253319 A1	12/2004	Netke et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2004/0259817 A1	12/2004	Waldon et al.	2006/0135619 A1	6/2006	Kick et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0165744 A1	7/2006	Jamil et al.
2005/0003003 A1	1/2005	Basu et al.	2006/0193789 A1	8/2006	Tamarkin et al.
2005/0004088 A1	1/2005	Hesch	2006/0194775 A1	8/2006	Tofovic et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2006/0204557 A1	9/2006	Gupta et al.
2005/0014729 A1	1/2005	Pulaski	2006/0233743 A1	10/2006	Kelly
2005/0020550 A1	1/2005	Morris et al.	2006/023841 A1	10/2006	Brodbeck et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2006/0235037 A1	10/2006	Purandare et al.
2005/0021009 A1	1/2005	Massara et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0025833 A1	2/2005	Aschkenasy et al.	2006/0246122 A1	11/2006	Langguth et al.
2005/0031651 A1	2/2005	Gervais et al.	2006/0247216 A1	11/2006	Haj-Yehia
2005/0042173 A1	2/2005	Besse et al.	2006/0247221 A1	11/2006	Coelingh Bennink et al.
2005/0042268 A1	2/2005	Aschkenasy et al.	2006/0251581 A1	11/2006	McIntyre et al.
2005/0048116 A1	3/2005	Straub et al.	2006/0252049 A1	11/2006	Shuler et al.
2005/0054991 A1	3/2005	Tobyn et al.	2006/0257472 A1	11/2006	Nielsen
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0275218 A1	12/2006	Tamarkin et al.
2005/0085453 A1	4/2005	Govindarajan	2006/0275360 A1	12/2006	Ahmed et al.
2005/0101579 A1	5/2005	Shippen	2006/0276414 A1	12/2006	Coelingh Bennink et al.
2005/0113350 A1	5/2005	Duesterberg et al.	2006/0280771 A1	12/2006	Groenewegen et al.
2005/0118244 A1	6/2005	Theobald et al.	2006/0280797 A1	12/2006	Shoichet et al.
2005/0118272 A1	6/2005	Besse et al.	2006/0280800 A1	12/2006	Nagi et al.
2005/0129756 A1	6/2005	Podhaisky et al.	2006/0292223 A1	12/2006	Woolfson et al.
2005/0152956 A1	7/2005	Dudley	2007/0004693 A1	1/2007	Woolfson et al.
2005/0153946 A1	7/2005	Hirsh et al.	2007/0004694 A1	1/2007	Woolfson et al.
2005/0164977 A1	7/2005	Coelingh Bennink	2007/0009559 A1	1/2007	Li et al.
2005/0182105 A1	8/2005	Nirschl et al.	2007/0009594 A1	1/2007	Grubb et al.
2005/0186141 A1	8/2005	Gonda et al.	2007/0010550 A1	1/2007	McKenzie
2005/0187267 A1	8/2005	Hamann et al.	2007/0014839 A1	1/2007	Bracht
2005/0192253 A1	9/2005	Salvati et al.	2007/0015698 A1	1/2007	Kleinman et al.
2005/0192310 A1	9/2005	Gavai et al.	2007/0021360 A1	1/2007	Nyce et al.
2005/0196434 A1	9/2005	Briere	2007/0027201 A1	2/2007	McComas et al.
2005/0207990 A1	9/2005	Funke et al.	2007/0031491 A1	2/2007	Levine et al.
2005/0214384 A1	9/2005	Juturu et al.	2007/0037780 A1	2/2007	Ebert et al.
2005/0220825 A1	10/2005	Funke et al.	2007/0037782 A1	2/2007	Hibino et al.
2005/0220900 A1	10/2005	Popp et al.	2007/0042038 A1	2/2007	Besse
2005/0222106 A1	10/2005	Bracht	2007/0060589 A1	3/2007	Purandare et al.
2005/0239747 A1	10/2005	Yang et al.	2007/0066628 A1	3/2007	Zhang et al.
2005/0239758 A1	10/2005	Roby	2007/0066637 A1	3/2007	Zhang et al.
2005/0244360 A1	11/2005	Billoni	2007/0066675 A1	3/2007	Zhang et al.
2005/0244522 A1	11/2005	Carrara et al.	2007/0078091 A1	4/2007	Hubler et al.
2005/0245902 A1	11/2005	Cornish et al.	2007/0088029 A1	4/2007	Balog et al.
2005/0250746 A1	11/2005	Iammatteo	2007/0093548 A1	4/2007	Diffendal et al.
2005/0250750 A1	11/2005	Cummings et al.	2007/0116729 A1	5/2007	Palepu
2005/0250753 A1	11/2005	Fink et al.	2007/0116829 A1	5/2007	Prakash et al.
2005/0256028 A1	11/2005	Yun et al.	2007/0128263 A1	6/2007	Gargiulo et al.
2005/0266078 A1	12/2005	Jorda et al.	2007/0154533 A1	7/2007	Dudley
2005/0266088 A1	12/2005	Hinrichs et al.	2007/0167418 A1	7/2007	Ferguson
2005/0271597 A1	12/2005	Keith	2007/0178166 A1	8/2007	Bernstein et al.
2005/0271598 A1	12/2005	Frieman et al.	2007/0184558 A1	8/2007	Roth et al.
2005/0272685 A1	12/2005	Hung	2007/0186433 A1	8/2007	Ron et al.
2005/0272712 A1	12/2005	Grubb et al.	2007/0207225 A1	9/2007	Squadrito
2006/0009428 A1	1/2006	Grubb et al.	2007/0225281 A1	9/2007	Zhang et al.
2006/0014728 A1	1/2006	Chwalisz et al.	2007/0232574 A1	10/2007	Galey et al.
2006/0018937 A1	1/2006	Friedman et al.	2007/0238713 A1	10/2007	Gast et al.
2006/0019978 A1	1/2006	Balog	2007/0243229 A1	10/2007	Smith et al.
2006/0020002 A1	1/2006	Salvati et al.	2007/0248658 A1	10/2007	Zurdo Schroeder et al.
2006/0030615 A1	2/2006	Fensome et al.	2007/0254858 A1	11/2007	Cronk
2006/0034889 A1	2/2006	Jo et al.	2007/0255197 A1	11/2007	Humberstone et al.
2006/0034904 A1	2/2006	Weimann	2007/0264309 A1	11/2007	Chollet et al.
2006/0051391 A1	3/2006	Dvoskin et al.	2007/0264345 A1	11/2007	Eros et al.
2006/0052341 A1	3/2006	Cornish et al.	2007/0264349 A1	11/2007	Lee et al.
2006/0069031 A1	3/2006	Loumaye	2007/0286819 A1	12/2007	DeVries et al.
2006/0078618 A1	4/2006	Constantinides et al.	2007/0287688 A1	12/2007	Chan et al.
2006/0083778 A1	4/2006	Allison et al.	2007/0287789 A1	12/2007	Jones et al.
2006/0084704 A1	4/2006	Shih et al.	2007/0292359 A1	12/2007	Friedman et al.
2006/0088580 A1	4/2006	Meconi et al.	2007/0292387 A1	12/2007	Jon et al.

US 9,006,222 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2007/0292461 A1	12/2007	Tamarkin et al.	2009/0214474 A1	8/2009	Jennings
2007/0292493 A1	12/2007	Brierre	2009/0227025 A1	9/2009	Nichols et al.
2007/0298089 A1	12/2007	Saeki et al.	2009/0227550 A1	9/2009	Mattern
2008/0026035 A1	1/2008	Chollet et al.	2009/0232897 A1	9/2009	Sahoo et al.
2008/0026040 A1	1/2008	Farr et al.	2009/0258096 A1	10/2009	Cohen
2008/0026062 A1	1/2008	Farr et al.	2009/0264395 A1	10/2009	Creasy et al.
2008/0038219 A1	2/2008	Mosbaugh et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0038350 A1	2/2008	Gerecke et al.	2009/0285772 A1	11/2009	Phasivongsa et al.
2008/0039405 A1	2/2008	Langley et al.	2009/0285869 A1	11/2009	Trimble
2008/0050317 A1	2/2008	Tamarkin et al.	2009/0318558 A1	12/2009	Kim et al.
2008/0051351 A1	2/2008	Ghisalberti	2009/0324714 A1	12/2009	Liu et al.
2008/0063607 A1	3/2008	Tamarkin et al.	2009/0325916 A1	12/2009	Zhang et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0069791 A1	3/2008	Beissert	2010/0028360 A1	2/2010	Atwood
2008/0085877 A1	4/2008	Bortz	2010/0034838 A1	2/2010	Staniforth et al.
2008/0095831 A1	4/2008	McGraw	2010/0034880 A1	2/2010	Sintov et al.
2008/0095838 A1	4/2008	Abou Chakra-Vernet	2010/0040671 A1	2/2010	Ahmed et al.
2008/0113953 A1	5/2008	DeVries et al.	2010/0048523 A1	2/2010	Bachman et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0055138 A1	3/2010	Margulies et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0074959 A1	3/2010	Hansom et al.
2008/0125402 A1	5/2008	Diliberti et al.	2010/0086501 A1	4/2010	Chang et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0086599 A1	4/2010	Huempel et al.
2008/0138390 A1	6/2008	Hsu et al.	2010/0092568 A1	4/2010	Lerner et al.
2008/0139392 A1	6/2008	Acosta Zara et al.	2010/0119585 A1	5/2010	Hille et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0129320 A1	5/2010	Phasivongsa et al.
2008/0153789 A1	6/2008	Dmowski et al.	2010/0105071 A1	6/2010	Chen et al.
2008/0175814 A1	7/2008	Phasivongsa et al.	2010/0136105 A1	6/2010	Chen et al.
2008/0175905 A1	7/2008	Liu et al.	2010/0137265 A1	6/2010	Leonard
2008/0175908 A1	7/2008	Liu et al.	2010/0137271 A1	6/2010	Chen et al.
2008/0188829 A1	8/2008	Creasy	2010/0143420 A1	6/2010	Shenoy et al.
2008/0206156 A1	8/2008	Cronk	2010/0143481 A1	6/2010	Shenoy et al.
2008/0206159 A1	8/2008	Tamarkin et al.	2010/0150993 A1	6/2010	Theobald et al.
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0152144 A1	6/2010	Hermsmeyer
2008/0214512 A1	9/2008	Seitz et al.	2010/0168228 A1	7/2010	Bose et al.
2008/0220069 A1	9/2008	Allison	2010/0183723 A1	7/2010	Laurent-Applegate
2008/0226698 A1	9/2008	Tang et al.	2010/0184736 A1	7/2010	Coelingh Bennink et al.
2008/0227763 A1	9/2008	Lanquetin et al.	2010/0190758 A1	7/2010	Fauser et al.
2008/0234199 A1	9/2008	Katamreddym et al.	2010/0204326 A1	8/2010	D Souza
2008/0234240 A1	9/2008	Duesterberg et al.	2010/0210994 A1	8/2010	Zarif
2008/0255078 A1	10/2008	Katamreddym et al.	2010/0221195 A1	9/2010	Tamarkin et al.
2008/0255089 A1	10/2008	Katamreddym et al.	2010/0227797 A1	9/2010	Axelson et al.
2008/0261931 A1	10/2008	Hedner et al.	2010/0240626 A1	9/2010	Kulkarni et al.
2008/0299220 A1	12/2008	Tamarkin et al.	2010/0247482 A1	9/2010	Cui et al.
2008/0306036 A1	12/2008	Katamreddym et al.	2010/0247632 A1	9/2010	Dong et al.
2008/0312197 A1	12/2008	Rodriguez	2010/0247635 A1	9/2010	Rosenberg et al.
2008/0312198 A1	12/2008	Rodriguez	2010/0255085 A1	10/2010	Liu et al.
2008/0319078 A1	12/2008	Katamreddym et al.	2010/0273730 A1	10/2010	Hsu et al.
2009/0004246 A1	1/2009	Woolfson et al.	2010/0278759 A1	11/2010	Murad
2009/0010968 A1	1/2009	Allart et al.	2010/0279988 A1	11/2010	Setiawan et al.
2009/0011041 A1	1/2009	Musaeva et al.	2010/0291191 A1	11/2010	Shoichet et al.
2009/0017120 A1	1/2009	Trimble et al.	2010/0292199 A1	11/2010	Leverd et al.
2009/0022683 A1	1/2009	Song et al.	2010/0303825 A9	12/2010	Sirbasku et al.
2009/0047357 A1	2/2009	Tomohira et al.	2010/0312137 A1	12/2010	Gilmour et al.
2009/0053294 A1	2/2009	Prendergast	2010/0316724 A1	12/2010	Whitfield et al.
2009/0060982 A1	3/2009	Ron et al.	2010/0322884 A1	12/2010	Dipietro et al.
2009/0060997 A1	3/2009	Seitz et al.	2010/0330168 A1	12/2010	Gicquel et al.
2009/0068118 A1	3/2009	Eini et al.	2011/0028439 A1	2/2011	Witt-Enderby et al.
2009/0081206 A1	3/2009	Leibovitz	2011/0039814 A1	2/2011	Huatan et al.
2009/0081278 A1	3/2009	De Graaff et al.	2011/0053845 A1	3/2011	Levine et al.
2009/0081303 A1	3/2009	Savoir et al.	2011/0076775 A1	3/2011	Stewart et al.
2009/0092656 A1	4/2009	Klamerus et al.	2011/0076776 A1	3/2011	Stewart et al.
2009/0093440 A1	4/2009	Murad	2011/0086825 A1	4/2011	Chatroux
2009/0098069 A1	4/2009	Vacca	2011/0087192 A1	4/2011	Uhlund et al.
2009/0099106 A1	4/2009	Phasivongsa et al.	2011/0091555 A1	4/2011	De Luigi Bruschi et al.
2009/0099149 A1	4/2009	Liu et al.	2011/0098258 A1	4/2011	Masini Eteve et al.
2009/0130029 A1	5/2009	Tamarkin et al.	2011/0098631 A1	4/2011	McIntyre et al.
2009/0131385 A1	5/2009	Voskuhl	2011/0104268 A1	5/2011	Pachot et al.
2009/0137478 A1	5/2009	Bernstein et al.	2011/0104289 A1	5/2011	Savoir Vilboeuf et al.
2009/0137538 A1	5/2009	Klamerus et al.	2011/0130372 A1	6/2011	Agostinacchio et al.
2009/0143344 A1	6/2009	Chang	2011/0135719 A1	6/2011	Besins et al.
2009/0175799 A1	7/2009	Tamarkin et al.	2011/0142945 A1	6/2011	Chen et al.
2009/0181088 A1	7/2009	Song et al.	2011/0152840 A1	6/2011	Lee et al.
2009/0186081 A1	7/2009	Holm et al.	2011/0158920 A1	6/2011	Morley et al.
2009/0197843 A1	8/2009	Notelovitz et al.	2011/0171140 A1	7/2011	Illum et al.
2009/0203658 A1	8/2009	Marx et al.	2011/0182997 A1	7/2011	Lewis et al.
			2011/0190201 A1	8/2011	Hyde et al.
			2011/0195031 A1	8/2011	Du
			2011/0195114 A1	8/2011	Carrara et al.
			2011/0195944 A1	8/2011	Mura et al.

US 9,006,222 B2

Page 8

(56)	References Cited			
U.S. PATENT DOCUMENTS				
2011/0217341 A1	9/2011 Sah	2013/0004619 A1	1/2013 Chow et al.	
2011/0238003 A1	9/2011 Bruno Raimondi et al.	2013/0011342 A1	1/2013 Tamarkin et al.	
2011/0244043 A1	10/2011 Xu et al.	2013/0017239 A1	1/2013 Viladot Petit et al.	
2011/0250256 A1	10/2011 Hyun Oh et al.	2013/0022674 A1	1/2013 Dudley et al.	
2011/0250259 A1	10/2011 Buckman	2013/0023505 A1	1/2013 Garfield et al.	
2011/0250274 A1	10/2011 Shaked et al.	2013/0023823 A1	1/2013 Simpson et al.	
2011/0256092 A1	10/2011 Phiasivongsa et al.	2013/0028850 A1	1/2013 Tamarkin et al.	
2011/0262373 A1	10/2011 Umbert Millet	2013/0029947 A1	1/2013 Nachaegari et al.	
2011/0262494 A1	10/2011 Achleitner et al.	2013/0029957 A1	1/2013 Giliyar et al.	
2011/0268665 A1	11/2011 Tamarkin et al.	2013/0045266 A1	2/2013 Choi et al.	
2011/0275584 A1	11/2011 Wilckens et al.	2013/0045953 A1	2/2013 Sitruk Ware et al.	
2011/0281832 A1	11/2011 Li et al.	2013/0059795 A1	3/2013 Lo et al.	
2011/0287094 A1	11/2011 Penhasi et al.	2013/0064897 A1	3/2013 Binay	
2011/0293720 A1	12/2011 General et al.	2013/0072466 A1	3/2013 Choi et al.	
2011/0294738 A1	12/2011 Ren et al.	2013/0084257 A1	4/2013 Ishida et al.	
2011/0300167 A1	12/2011 McMurry et al.	2013/0085123 A1	4/2013 Li et al.	
2011/0301087 A1	12/2011 McBride et al.	2013/0089574 A1	4/2013 Schmidt Gollwitzer et al.	
2011/0306579 A1	12/2011 Stein	2013/0090318 A1	4/2013 Ullmann et al.	
2011/0311592 A1	12/2011 Birbara	2013/0102781 A1	4/2013 Bevill et al.	
2011/0312927 A1	12/2011 Nachaegari et al.	2013/0108551 A1	5/2013 Langereis et al.	
2011/0312928 A1	12/2011 Nachaegari et al.	2013/0116215 A1	5/2013 Coma et al.	
2011/0318405 A1	12/2011 Erwin	2013/0116222 A1	5/2013 Arnold et al.	
2011/0318431 A1	12/2011 Gulati	2013/0122051 A1	5/2013 Abidi et al.	
2012/0009276 A1	1/2012 De Groot	2013/0123175 A1	5/2013 Hill et al.	
2012/0015350 A1	1/2012 Nabatiyan et al.	2013/0123220 A1	5/2013 Queiroz	
2012/0021041 A1	1/2012 Rossi et al.	2013/0123351 A1	5/2013 Dewitt	
2012/0028888 A1	2/2012 Janz et al.	2013/0164225 A1	6/2013 Tamarkin et al.	
2012/0028910 A1	2/2012 Combal et al.	2013/0164346 A1	6/2013 Lee et al.	
2012/0028936 A1	2/2012 Gloger et al.	2013/0165744 A1	6/2013 Carson et al.	
2012/0045532 A1	2/2012 Cohen	2013/0178452 A1	7/2013 King	
2012/0046264 A1	2/2012 Simes et al.	2013/0183254 A1	7/2013 Zhou et al.	
2012/0046518 A1	2/2012 Yoakum et al.	2013/0183325 A1	7/2013 Bottoni et al.	
2012/0269878 A2	2/2012 Cantor et al.	2013/0189193 A1	7/2013 Tamarkin et al.	
2012/0052077 A1	3/2012 Truitt et al.	2013/0189196 A1	7/2013 Tamarkin et al.	
2012/0058171 A1	3/2012 De Graaff et al.	2013/0189230 A1	7/2013 Shoichet et al.	
2012/0058962 A1	3/2012 Cumming et al.	2013/0189368 A1	7/2013 Mosqueira et al.	
2012/0058979 A1	3/2012 Keith et al.	2013/0210709 A1	8/2013 McMurry et al.	
2012/0064135 A1	3/2012 Levin et al.	2013/0216550 A1	8/2013 Penninger et al.	
2012/0065179 A1	3/2012 Andersson	2013/0216596 A1	8/2013 Viladot Petit et al.	
2012/0087872 A1	4/2012 Tamarkin et al.	2013/0224177 A1	8/2013 Kim et al.	
2012/0101073 A1	4/2012 Mannion et al.	2013/0224257 A1	8/2013 Sah et al.	
2012/0121517 A1	5/2012 Song et al.	2013/0224268 A1	8/2013 Alam et al.	
2012/0121692 A1	5/2012 Xu et al.	2013/0224300 A1	8/2013 Maggio	
2012/0122829 A1	5/2012 Taravella et al.	2013/0225412 A1	8/2013 Sardari Lodriche et al.	
2012/0128625 A1	5/2012 Shalwitz et al.	2013/0225542 A1	8/2013 Poegh et al.	
2012/0128654 A1	5/2012 Terpstra et al.	2013/0226113 A1	8/2013 Schumacher et al.	
2012/0128683 A1	5/2012 Shantha	2013/0243696 A1	9/2013 Wang et al.	
2012/0128733 A1	5/2012 Perrin et al.	2013/0245253 A1	9/2013 Marx et al.	
2012/0128777 A1	5/2012 Keck et al.	2013/0245570 A1	9/2013 Jackson	
2012/0129773 A1	5/2012 Geier et al.	2013/0261096 A1	10/2013 Merian et al.	
2012/0129819 A1	5/2012 Vancaillie et al.	2013/0266645 A1	10/2013 Becker et al.	
2012/0136013 A1	5/2012 Li et al.	2013/0267485 A1	10/2013 Da Silva Maia Filho	
2012/0142645 A1	6/2012 Marx	2013/0273167 A1	10/2013 Lee et al.	
2012/0148670 A1	6/2012 Kim et al.	2013/0274211 A1	10/2013 Burman et al.	
2012/0149748 A1	6/2012 Shanler et al.	2013/0280213 A1	10/2013 Voskuhl	
2012/0172343 A1	7/2012 Lindenthal et al.	2013/0316374 A1	11/2013 Penninger et al.	
2012/0184515 A1	7/2012 Klar et al.	2013/0317065 A1	11/2013 Tatani et al.	
2012/0231052 A1	9/2012 Sitruk Ware et al.	2013/0317315 A1	11/2013 Lu et al.	
2012/0232011 A1	9/2012 Kneissel et al.	2013/0324565 A1	12/2013 Li et al.	
2012/0232042 A1	9/2012 Klar et al.	2013/0331363 A1	12/2013 Li et al.	
2012/0263679 A1	10/2012 Marlow et al.	2013/0338124 A1	12/2013 Li et al.	
2012/0269721 A1	10/2012 Weng et al.	2013/0345187 A1	12/2013 Rodriguez Oquendo	
2012/0277249 A1	11/2012 Andersson et al.	2014/0018335 A1	1/2014 Tatani et al.	
2012/0277727 A1	11/2012 Doshi et al.	2014/0024590 A1	1/2014 Weidhaas et al.	
2012/0283671 A1	11/2012 Shibata et al.	2014/0031289 A1	1/2014 Song et al.	
2012/0295911 A1	11/2012 Mannion et al.	2014/0031323 A1	1/2014 Perez	
2012/0301517 A1	11/2012 Zhang et al.	2014/0066416 A1	3/2014 Leunis et al.	
2012/0301538 A1	11/2012 Gordon Beresford et al.	2014/0072531 A1	3/2014 Kim et al.	
2012/0302535 A1	11/2012 Caufriez et al.	2014/0079686 A1	3/2014 Barman et al.	
2012/0316130 A1	12/2012 Hendrix	2014/0088058 A1	3/2014 Maurizio	
2012/0316496 A1	12/2012 Hoffmann et al.	2014/0088059 A1	3/2014 Perumal et al.	
2012/0321579 A1	12/2012 Edelson et al.	2014/0094426 A1	4/2014 Drummond et al.	
2012/0322779 A9	12/2012 Voskuhl	2014/0100159 A1	4/2014 Conrad	
2012/0328549 A1	12/2012 Edelson et al.	2014/0100206 A1	4/2014 Bernick et al.	
2012/0329738 A1	12/2012 Liu			

US 9,006,222 B2

Page 9

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2014/0113889	A1	4/2014	Connor et al.	WO	2004017983	A1
2014/0127185	A1	5/2014	Stein et al.	WO	2005027911	A1
2014/0127280	A1	5/2014	Duesterberg et al.	WO	2004032897	A2
2014/0127308	A1	5/2014	Opara et al.	WO	2004052336	A2
2014/0128798	A1	5/2014	Janson et al.	WO	2004054540	A2
2014/0148491	A1	5/2014	Valia et al.	WO	2004080413	A2
2014/0186332	A1	7/2014	Ezrin et al.	WO	2005030175	A1
2014/0187487	A1	7/2014	Shoichet et al.	WO	2005087194	A1
2014/0193523	A1	7/2014	Henry	WO	2005087199	A2
2014/0194396	A1	7/2014	Li et al.	WO	20060113369	A2
2014/0206616	A1	7/2014	Ko et al.	WO	2006034090	A1
				WO	2006036899	A2
FOREIGN PATENT DOCUMENTS						
EP	0275716	A1	7/1988	WO	2006053172	A2
EP	0622075	A1	11/1994	WO	2006105615	A1
EP	0785211	A1	1/1996	WO	2006113505	A2
EP	0811381	A1	6/1997	WO	2006138686	A1
EP	0785212	A1	7/1997	WO	2006138735	A2
EP	1094781	B1	7/2008	WO	2007045027	A1
EP	2191833	A1	6/2010	WO	2007103294	A2
GB	1589946	A1	2/1921	WO	WO2007120868	10/2007
GB	452238	A	8/1936	WO	2007123790	A1
GB	720561	A	12/1954	WO	2007124250	A2
GB	848881	A	9/1960	WO	2007144151	A1
GB	874368	A	8/1961	WO	2008049516	A3
IN	216026	A	3/2008	WO	2008152444	A2
IN	2005KO00053	A	9/2009	WO	2009002542	A1
IN	244217	A	11/2010	WO	2009036311	A1
WO	9011064	A1	10/1990	WO	2009040818	4/2009
WO	9317686	A1	9/1993	WO	2009069006	A2
WO	9422426	A1	10/1994	WO	2009098072	A2
WO	9530409	A1	11/1995	WO	2009133352	A2
WO	9609826	A2	4/1996	WO	2010033188	A2
WO	WO619975		7/1996	WO	WO2010146872	11/2009
WO	9630000	A1	10/1996	WO	2011000210	A1
WO	9705491		2/1997	WO	2011073995	A2
WO	9743989	A1	11/1997	WO	2011120084	A1
WO	9810293	A1	3/1998	WO	2011128336	A1
WO	9832465	A1	7/1998	WO	2012009778	A2
WO	9851280	A1	11/1998	WO	2012024361	A1
WO	9932072	A1	7/1999	WO	WO2012055814	A1
WO	9939700	A1	8/1999	WO	WO2012065740	5/2012
WO	9942109	A1	8/1999	WO	WO2012098090	A1
WO	9943304		9/1999	WO	WO2012116277	A1
WO	9948477	A1	9/1999	WO	WO2012118563	A2
WO	9953910	A2	10/1999	WO	WO2012120365	A1
WO	0038659	A1	11/1999	WO	WO2012127501	A2
WO	9963974	A2	12/1999	WO	WO2012156561	A1
WO	0001351	A1	1/2000	WO	WO2012156822	A1
WO	0006175	A1	2/2000	WO	WO2012158483	A2
WO	0045795	A2	8/2000	WO	WO2012166909	A1
WO	0050007	A1	8/2000	WO	WO2012170578	A1
WO	0059577	A1	10/2000	WO	WO2013011501	A1
WO	0137808	A1	11/2000	WO	WO2013025449	A1
WO	0076522	A1	12/2000	WO	WO2013028639	A1
WO	0154699	A1	8/2001	WO	WO2013035101	A1
WO	0160325	A1	8/2001	WO	WO2013044067	A1
WO	0207700	A2	2/2002	WO	WO2013045404	A2
WO	0211768	A1	2/2002	WO	WO2013059285	A1
WO	0222132	A2	3/2002	WO	WO2013063279	A1
WO	0240008	A2	5/2002	WO	WO2013064620	A1
WO	WO0241878		5/2002	WO	WO2013071281	A1
WO	02053131	A1	7/2002	WO	WO2013088254	6/2013
WO	02078602	A2	10/2002	WO	WO2013102665	A1
WO	2002078604	A2	10/2002	WO	WO2013106437	A1
WO	WO03028667		4/2003	WO	WO2013113690	8/2013
WO	03041718	A1	5/2003	WO	WO2013124415	A1
WO	03041741	A1	5/2003	WO	WO2013127727	A1
WO	03068186	A1	8/2003	WO	WO2013127728	A1
WO	03077923	A1	9/2003	WO	WO2013144356	A1
WO	03082254	A1	10/2003	WO	WO2013149258	A2
WO	03092588	A2	11/2003	WO	WO2013158454	A2
WO	WO2004014432		2/2004	WO	WO2013170052	A1
				WO	2013192248	A1
						12/2013

US 9,006,222 B2

Page 10

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO 2013192249 A1 12/2013
 WO 2013192250 A1 12/2013
 WO 2013192251 A1 12/2013
 WO WO2013178587 A1 12/2013
 WO WO2013181449 A1 12/2013
 WO WO2014001904 A1 1/2014
 WO WO2014004424 A1 1/2014
 WO WO2014009434 A1 1/2014
 WO WO2014018569 A1 1/2014
 WO WO2014018570 A1 1/2014
 WO WO2014018571 A2 1/2014
 WO WO2014018856 A1 1/2014
 WO WO2014018932 A2 1/2014
 WO WO2014031958 A1 2/2014
 WO WO2014041120 A1 3/2014
 WO WO2014052792 A1 4/2014
 WO WO2014056897 A1 4/2014
 WO WO2014066442 A2 5/2014
 WO WO2014074846 A1 5/2014
 WO WO2014076231 A1 5/2014
 WO WO2014076569 A2 5/2014
 WO WO2014081598 A1 5/2014
 WO WO2014086739 A1 6/2014
 WO WO2014093114 A1 6/2014
 WO WO2014104784 A1 7/2014

OTHER PUBLICATIONS

- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Cendejas-Santana, G., et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C₂₁H₃₀O₂), desoxycorticosterone (C₂₁H₃₀O₃), corticosterone (C₂₁H₃₀O₄) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helveticae, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, Pharmaceutical Research, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, Journal of General Internal Medicine, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochimica Acta, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.

US 9,006,222 B2

Page 11

(56)

References Cited

OTHER PUBLICATIONS

- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzymiński, R. et al., EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnabik, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A. et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M. et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helveticae, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R. et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PhamSciTech, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
- Urian, Wulf H. et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T. et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. SteroidBiochem. Mol. Biol. (2013), Elsevier.
- Wiranichapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H. & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of *Thevetia peruviana* and *Hura crepitans* Seed oils using GC-FID, Fountain Journal of Nat. and Appl. Sciences, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro—Edible-Oil-Refining—ISO—TUV—Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, Sci. Agric., vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils In Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, Clean Techn Environ Policy, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, Obstetrics & Gynecology, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Suplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saftey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate—Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, Cereal Chem., vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- International Search Report and Written Opinion for related International Application No. PCT/US12/066406 dated Jan. 24, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046442 dated Nov. 1, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046443 dated Oct. 31, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046444 dated Oct. 31, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046445 dated Nov. 1, 2013.
- USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.
- USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.

US 9,006,222 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.
- Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.
- Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.
- Azure Pharma, Inc., "ELESTRINTM—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages (Aug. 2009).
- Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER_a and ER_b," Endocrinology, 149(10): 4857-4870 (Oct. 2008).
- Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).
- Tahition Noni, "Body Balance Cream," [http://products.tni.com/dominican_republic\(sa_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic(sa_spanish/nonistore/product/3438/3416/), (undated), 1 page.
- Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.
- Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).
- Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).
- Diramio, "Polyethylene Glycol Methacrylate/Dimethylacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia—Masters of Science Thesis, 131 pages (2004). http://athenaueum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1.
- Du, et al. "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 11, (Feb. 2013).
- Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.
- Fuchs, et al., "The Effects of on Estrogen and Glycolic Acid Cream on the Focal Skin of Postmenopausal Women: A Randomized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.
- Ganem-Quintana et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.
- Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.
- Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).
- Kincl, et al. "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.
- Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.
- Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Periestrual and Postinsemination Periods in Dairy Cattle," Biol Reprod. 35(2):300-311 (1986). Abstract Only.
- Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.
- NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.
- Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, min.sagepub.com. Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
- Panchagnula et al., "Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," J Pharm Pharmacol. 43(9):609-614 (Sep. 1991). Abstract Only.
- Patel, et al., "Transdermal Drug Delivery System: A Review," www.thepharmajournal.com, vol. 1 No. 4 2012.
- Salole, "The physicochemical properties of oestradiol," Journal of Pharmaceutical & Biomedical Analysis, 5 (7):635-648 (1987).
- Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," American Journal of Public Health, Published online ahead of print Jul. 18, 2013.
- Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014.
- Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," The American College of Obstetricians and Gynecologists, vol. 112, No. 5, Nov. 2008.
- Sitruk-Ware, et al., "Oral Micronized Progesterone," Department of Reproductive Endocrinology, vol. 36, No. 4, pp. 373-402, Oct. 1987.
- Sitruk-Ware, et al., "Progesterogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," Menopause: The Journal of the North American Menopause Society, vol. 9, No. 1, pp. 6-15, 2002.
- Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," JAMA Internal Medicine <http://archinte.jamanetwork.com>, Sep. 30, 2013.
- Stanczyk, et al. "Ethynodiol and 17 β -Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment," Departments of Obstetrics and Gynecology and Preventive Medicine, University of Southern California Keck School of Medicine, Contraception 87 706-727, (2013).
- Strickley, "Solvabilizing Excipients in Oral and Injectable Formulations," Pharmaceutical Research, 21(2):201-230 (Feb. 2004).
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," Skin Pharmacol Physiol, 19:106-121 (2006). http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf.
- Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," The British Medical Journal, vol. 280, No. 6217, Mar. 22, 1980.
- Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," Springer Science+Business Media B.V., Breast Cancer Res Treat 101:125-134, (2007).
- USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- ABITEC Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
- Gattefosse SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefosse SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.

US 9,006,222 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.
- Sullivan et al., "A review of the nonclinical safety of Transcetyl®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstatter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, Microchemical Journal 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, Journal of Steroid Biochemistry & Molecular Biology, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , Jour. of Pharm. Sci., vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, Pharmaceutical Research, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, Fertility and Sterility, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , Maturitas, The European Menopausal Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , Steroids, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, J Thermal Anal., vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , Journal of Animal Science, vol. 57, pp. 449-455, ISU, 1983.
- McGuffey, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, Chemistry and Industry, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, J. Steroid Biochem. Mol.Biol. (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, J. Pharmaceutical Sciences, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , Drug Devel. & Indust. Pharmacy,35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , Clinical Endocrinology, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, Arch Pharm Res, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , European Journal of Pharmaceutics and Biopharmaceutics, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, Crystal Structure Comm., Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, Intl. Jour. of Pharma., vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Pisegna, Gisela L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, Adv. Drug Delivery Reviews, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V., et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, Pharmaceutical Research, vol. 15(5) pp. 794-799,1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , J Steroids Horm Sci, 4:2, 2013.
- Satyana Rayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, Asian J. Chem., vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), J. Steroid Biochem.Mol. Biol. (2013), Elsevier.

US 9,006,222 B2

Page 14

(56)

References Cited

OTHER PUBLICATIONS

SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.
SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb 24, 2014, American Chem. Society.

Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.

Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.

Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.

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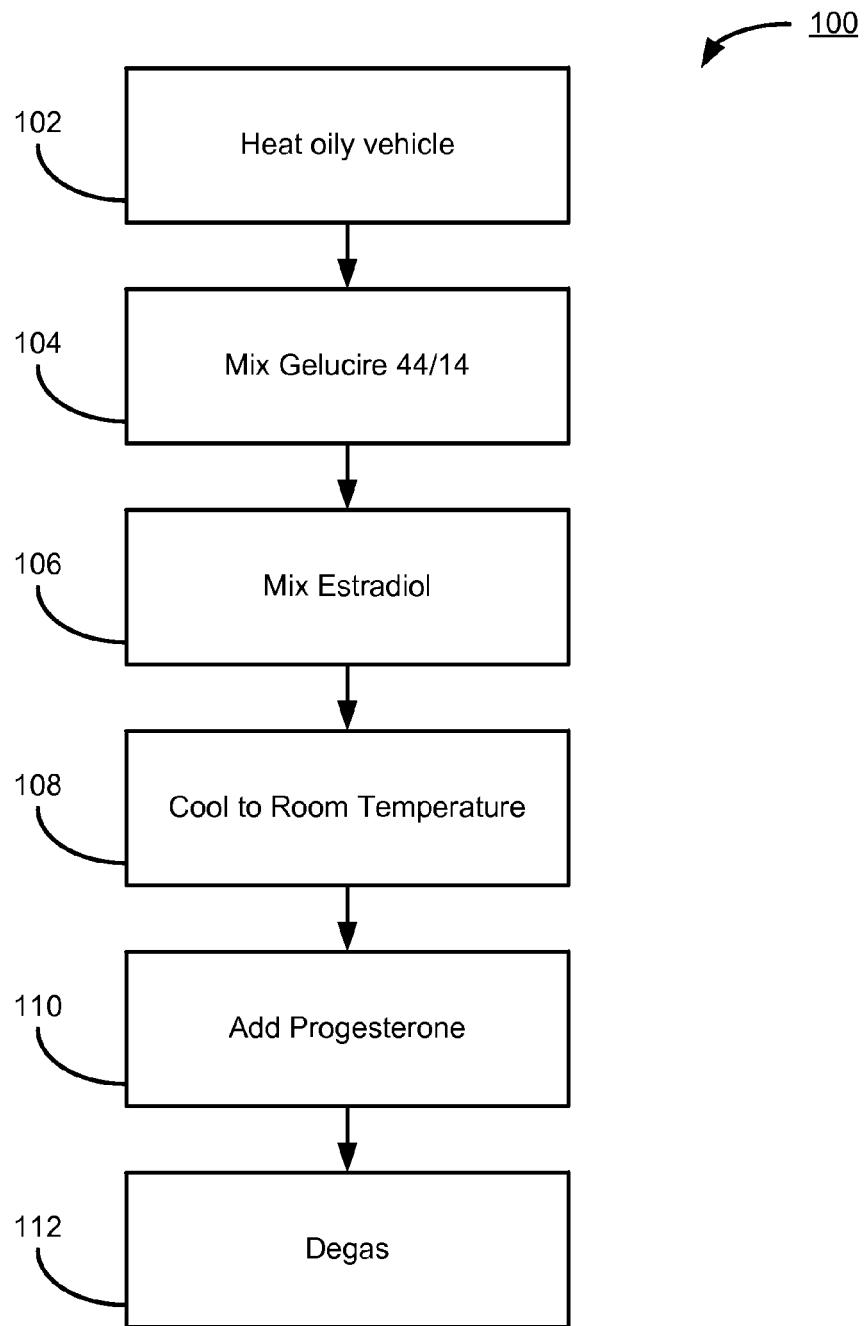


FIG. 1

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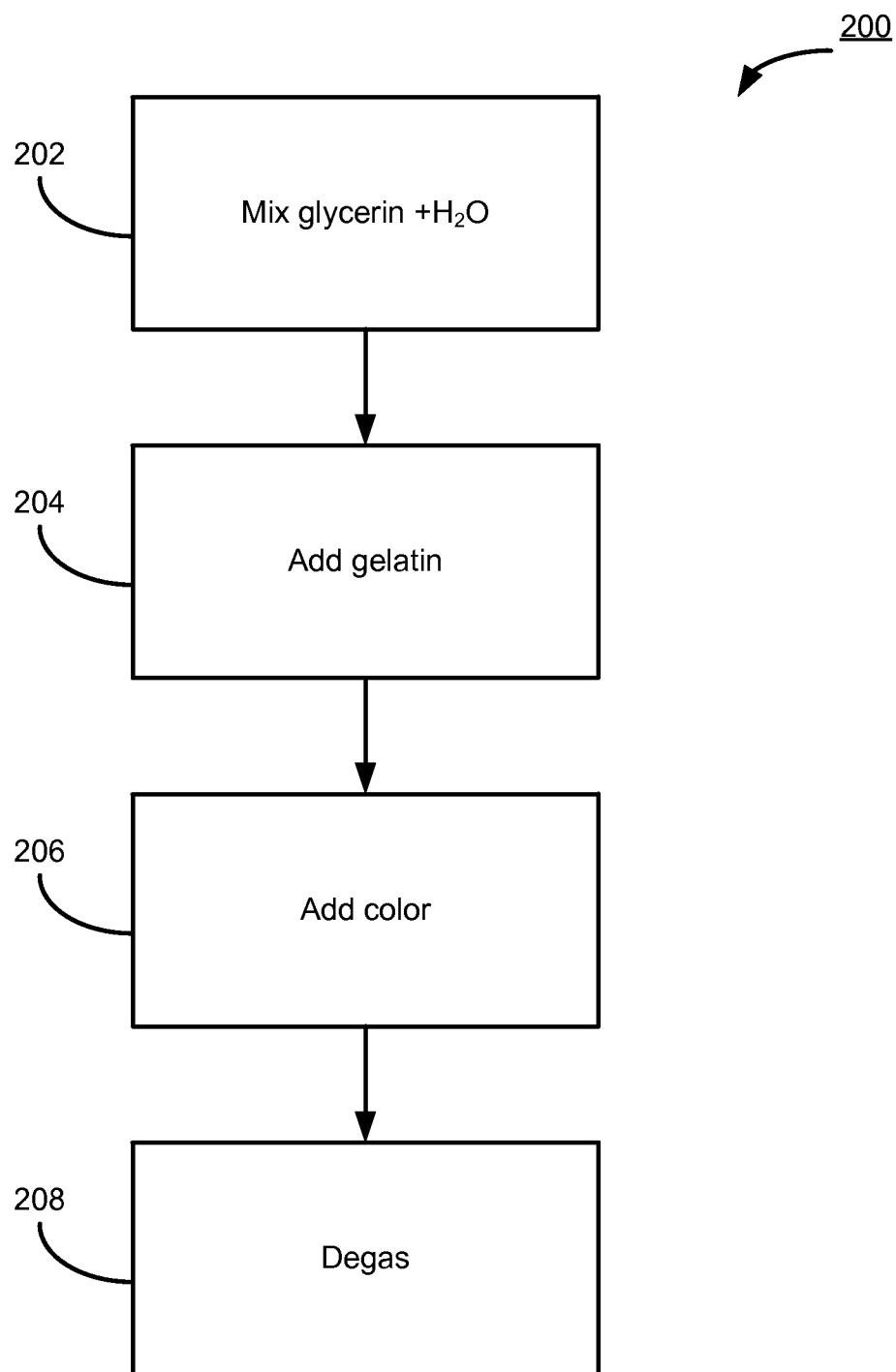


FIG. 2

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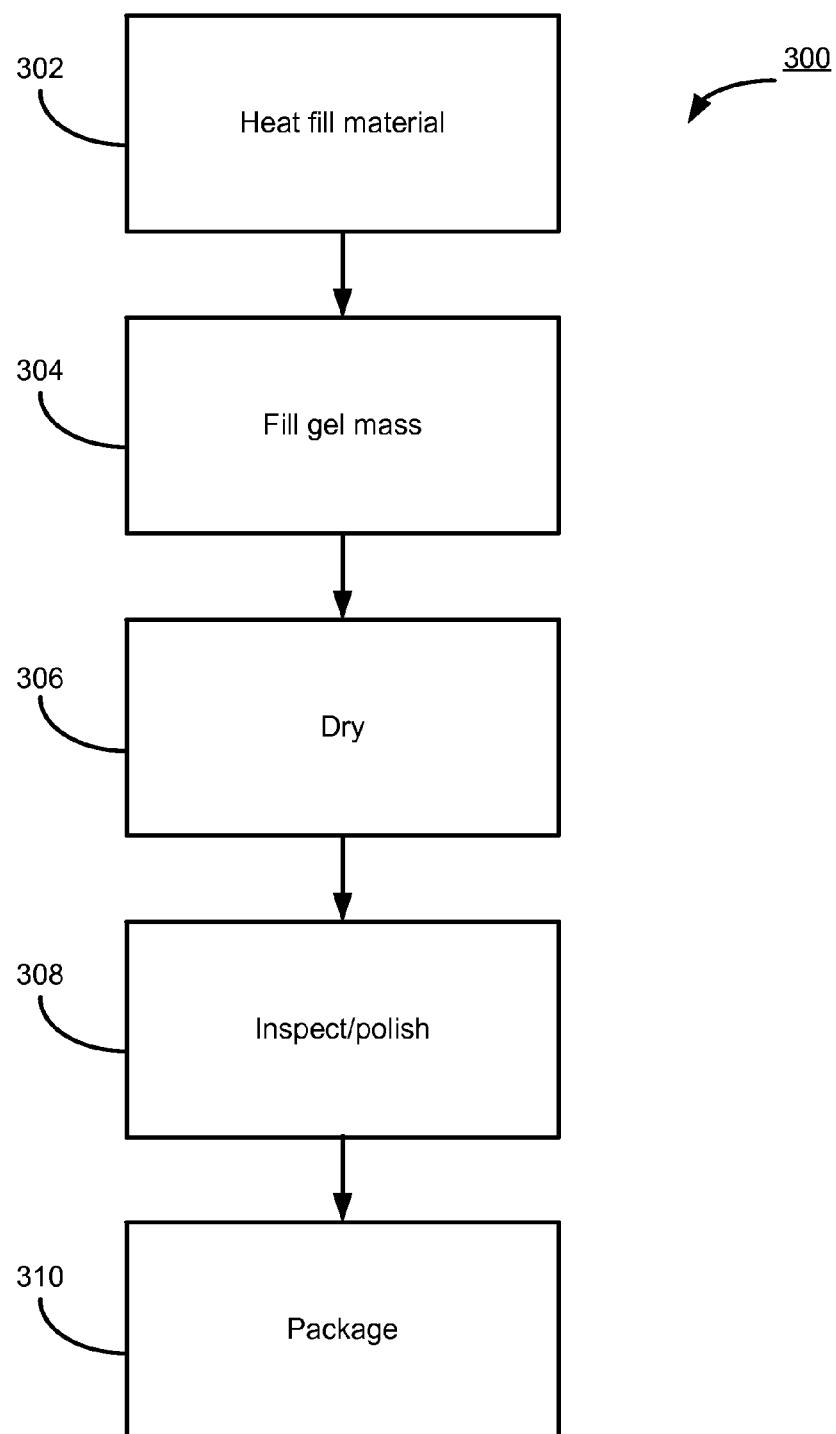


FIG. 3

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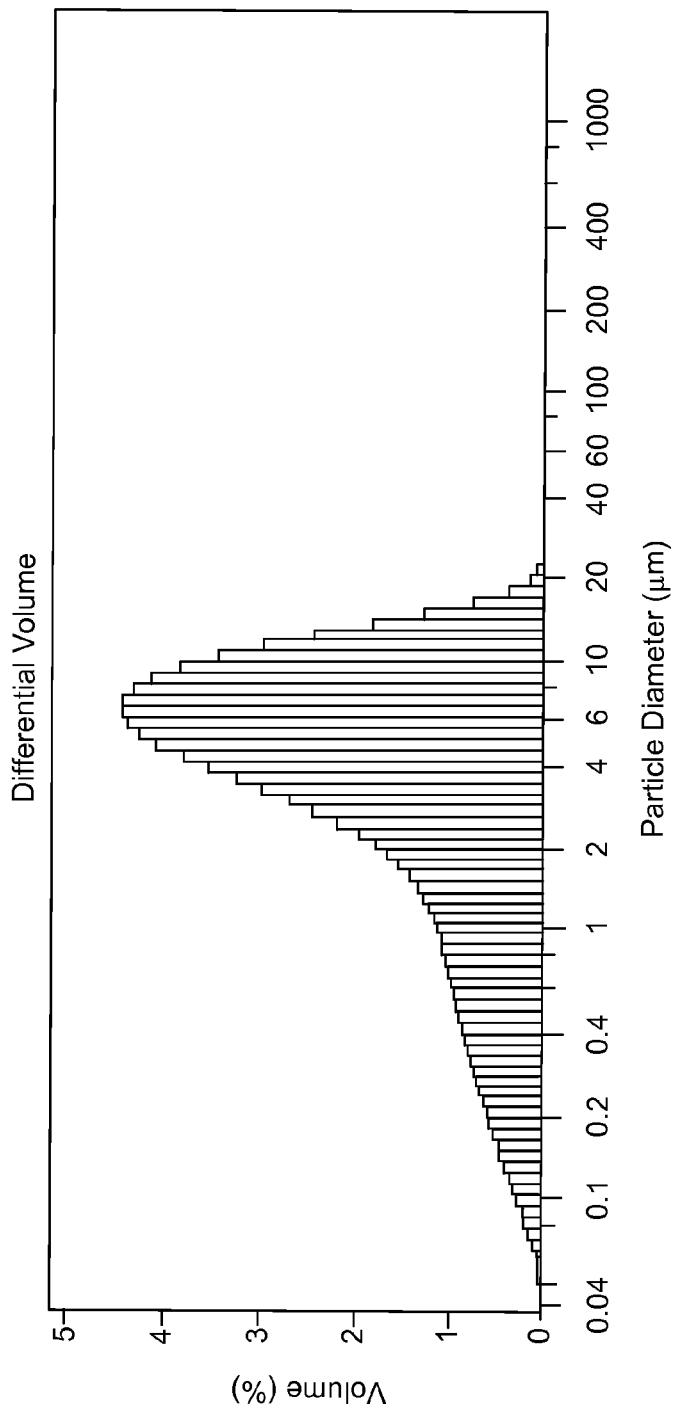


FIG. 4

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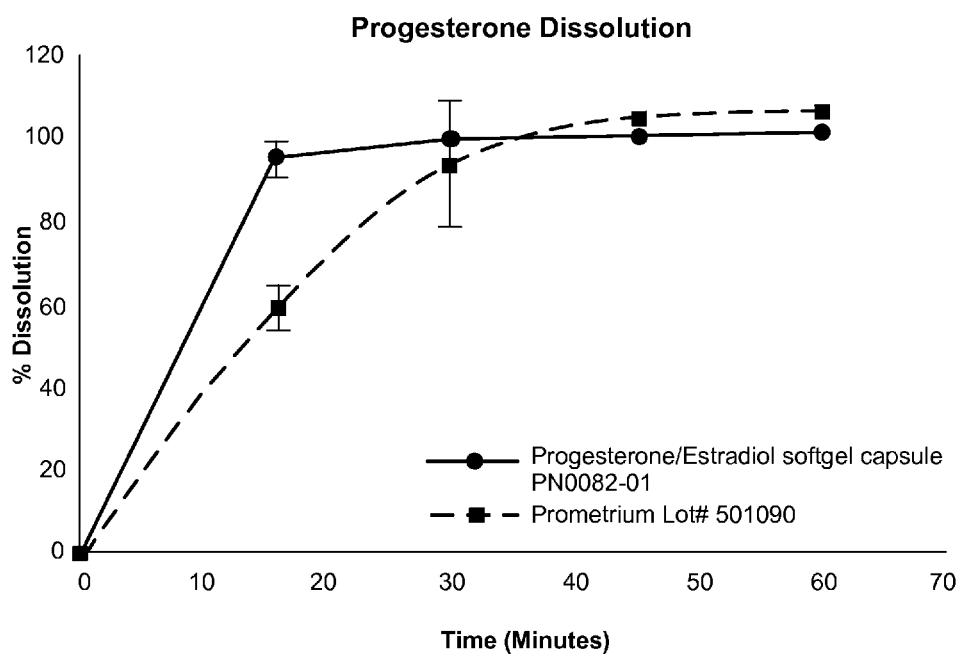


FIG. 5

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application claims priority to the following U.S. Patent Applications: U.S. application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES," which was filed on Nov. 21, 2012; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bod-

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ies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA #N019781. According to the prescribing information approved for this product (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

**BRIEF DESCRIPTION OF THE
DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, "Cmax" as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, "Tmax" as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, Cmax and, optionally, Tmax are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without

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limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution, i.e., at least 98% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be

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desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	Prometrium Capsules Daily Dose		
	100 mg	200 mg	300 mg
C _{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T _{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC ₀₋₁₀ (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions

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treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing

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zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol; Transcutol); diethylene glycol monoethyl ether; esters of saturated

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coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1.

The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g.,

Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid

esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated,

e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is

liquid at between room temperature and about 50 C, e.g., at or below 50 C, at or below 40 C, or at or below 50 C. In illustrative embodiments, Gelucire 44/14 is heated to about 65 C and Capmul MCM is heated to about 40 C to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium

chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others,

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Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monicaprylate, e.g., Capryol™ 90 (Gattefosse).

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20 C, are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

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In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefossé) and Labarafil® corn/apicot oil PEG-6 esters (Gattefossé).

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

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As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Formulation A- P: 50/EE: 0.25:		
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
Capmul MCM, NF	65.49	98.24
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00
Formulation B- P: 50/EE: 0.5:		
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
Capmul MCM, NF	65.32	97.98
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00
Formulation C - P: 100/EE: 0.5:		
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
Capmul MCM, NF	65.49	196.48
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00
Formulation D - P: 100/EE: 1:		
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
Capmul MCM, NF	65.32	195.97
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00
Formulation E- P: 200/EE: 2:		
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
Capmul MCM, NF	65.32	391.94
Gelucire 44/14, NF	1.00	6.00
Total	100.00	600.00

*Note:
1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

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In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

10 Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

15 According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. 20 Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

25 Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

30 Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

35 Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

40 Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use;

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reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES**Example 1****Estradiol Solubility**

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in Miglyol; ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labrasol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60

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TABLE 2-continued

Ingredient	Solubility (mg/g)
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

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TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethyl ether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the

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solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 5 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Myglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

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TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Campul MCM, NF	82.57	577.97	
Gelucire 44/14, NF	10.0	70.00	
TOTAL	100.00	700.00	

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Campul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Campul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

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Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm , an X75 of 17.3 μm , and an X25 of 5.3 gm. The Beckman Device also yielded that the mean particle size is 11.8 gm, the median particle size is 11.04 gm, the mode particle size is 13.6 gm, and the standard deviation is 7.8 gm.

Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:		100.00		700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65 C and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:		100.000		200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:		100.00		600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65 C and Capmul MCM is heated to 40 C +/- 5 C to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40 C; the mixture is then passed through a colloid mill, e.g., three times.

Example 15

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions.

This following study protocol was used to establish bioavailability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

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Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters Cmax, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

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Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Pharmacokinetic Parameter	Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)			
	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC _{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
AUC _{0-∞}	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters Cmax, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below for progesterone.

TABLE 19

Pharmacokinetic Parameter	Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)			
	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC _{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
AUC _{0-∞}	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

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Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Heating may be performed until the temperature reaches 80° C±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C. +/−3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C. +/−10° C. The wedge temperature may be 38° C. +/−3° C. The drum cooling temperature may be 4° C. +/−2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about

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120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

Example 17

Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @ 50° C. for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

40 The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

50 In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C, oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

Example 18

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second

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study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

We claim:

1. A pharmaceutical composition comprising:
a solubilizing agent, the solubilizing agent comprising an effective amount of a C6-C12 oil;

1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized in the solubilizing agent; and

100 mg progesterone;
wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

2. The pharmaceutical composition of claim 1, wherein the solubilizing agent is selected from at least one of monoglycerides, diglycerides, triglycerides, and combinations thereof, wherein the monoglycerides, diglycerides, and triglycerides are predominantly of C6-C12 fatty acid chain lengths.

3. The pharmaceutical composition of claim 2, wherein the monoglycerides, diglycerides, and triglycerides are >50% C6-C12 fatty acid chain lengths.

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4. A pharmaceutical composition comprising:
about 100 mg progesterone;
about 1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized;
about 195.97 mg of monoglycerides and diglycerides of caprylic acid and capric acid (CAPMUL MCM); and
about 3.0 mg of at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides (GELUCIRE 44/14);
wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

5. A method of treating a menopause-related symptom in a woman comprising administering an effective amount of pharmaceutical composition to a subject in need thereof, the pharmaceutical composition comprising:

about 100 mg progesterone;
about 1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized;

about 195.97 mg of monoglycerides and diglycerides of caprylic acid and capric acid (CAPMUL MCM); and

about 3.0 mg of at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides (GELUCIRE 44/14);
wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

6. The method of claim 5, wherein the pharmaceutical composition is administered as a continuous-combined therapy regimen.

7. The method of claim 5, wherein the pharmaceutical composition is administered a sequentially-combined therapy regimen.

8. A method of treating a vasomotor symptom in a woman comprising administering an effective amount of a pharmaceutical composition comprising:

1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized in the solubilizing agent;

100 mg progesterone; and

a solubilizing agent, the solubilizing agent comprising an effective amount of a C6-C12 oil;
wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent; and

wherein the pharmaceutical composition is administered once daily for the treatment of symptoms associated with menopause.

9. The method of claim 8, wherein the pharmaceutical composition is administered as a continuous-combined therapy regimen.

10. The method of claim 8, wherein the pharmaceutical composition is administered as a sequentially-combined therapy regimen.

11. The method of claim 8, wherein the solubilizing agent is selected from at least one of monoglycerides, diglycerides, triglycerides, and combinations thereof, wherein the monoglycerides, diglycerides, and triglycerides are predominantly of C6-C12 fatty acid chain lengths.

12. The method of claim 11, wherein the monoglycerides, diglycerides, and triglycerides are >50% C6-C12 fatty acid chain lengths.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,006,222 B2
APPLICATION NO. : 14/099623
DATED : April 14, 2015
INVENTOR(S) : Brian A. Bernick et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-fifth Day of June, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT H



US009114145B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 9,114,145 B2
(45) **Date of Patent:** *Aug. 25, 2015

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Neda Irani**, Palm Beach Garden, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/475,946**(22) Filed: **Sep. 3, 2014**(65) **Prior Publication Data**

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Related U.S. Application Data

- (60) Continuation of application No. 14/099,545, filed on Dec. 6, 2013, now Pat. No. 8,846,648, which is a division of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178.
- (60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

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(52) **U.S. Cl.**

CPC : *A61K 31/57* (2013.01); *A61K 9/16* (2013.01);
A61K 9/4858 (2013.01); *A61K 9/7023* (2013.01); *A61K 31/565* (2013.01)

(58) **Field of Classification Search**USPC 514/169; 424/452
See application file for complete search history.(56) **References Cited**

U.S. PATENT DOCUMENTS

2,232,438 A 2/1941 Butenandt
4,900,734 A * 2/1990 Maxson et al. 514/171
5,538,736 A 7/1996 Hoffmann et al.
5,556,635 A 9/1996 Istin et al.

5,580,572 A	12/1996	Mikler et al.
5,605,702 A	2/1997	Teillaud et al.
5,607,691 A	3/1997	Hale et al.
5,607,693 A	3/1997	Bonte et al.
5,609,617 A	3/1997	Shealy et al.
5,626,866 A	5/1997	Ebert et al.
5,653,983 A	8/1997	Meybeck et al.
5,660,839 A	8/1997	Allee et al.
5,662,927 A	9/1997	Ehrlich et al.
5,663,160 A	9/1997	Meybeck et al.
5,686,097 A	11/1997	Taskovich et al.
5,693,335 A	12/1997	Xia et al.
5,700,480 A	12/1997	Hille et al.
5,719,197 A	2/1998	Kanios et al.
5,770,220 A	6/1998	Meconi et al.
5,770,227 A	6/1998	Dong et al.
5,780,044 A	7/1998	Yewey et al.
5,780,050 A	7/1998	Jain et al.
5,788,984 A	8/1998	Guenther et al.
5,820,878 A	10/1998	Hirano et al.
5,840,327 A	11/1998	Gale et al.
5,843,468 A	12/1998	Burkoth et al.
5,843,979 A	12/1998	Wille et al.
5,858,394 A	1/1999	Lipp et al.
5,863,552 A	1/1999	Yue
5,882,676 A	3/1999	Lee et al.
5,885,612 A	3/1999	Meconi et al.
5,888,533 A	3/1999	Dunn

(Continued)

FOREIGN PATENT DOCUMENTS

WO	WO9619975	7/1996
WO	WO0241878	5/2002
WO	WO03028667	4/2003
WO	WO2004014432	2/2004
WO	WO2005081825	9/2005
WO	WO2007120868	10/2007
WO	WO2010146872	12/2010
WO	WO2012055814 A1	5/2012
WO	WO2012055840 A1	5/2012
WO	WO2012065740	5/2012

(Continued)

OTHER PUBLICATIONS

Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.

(Continued)

Primary Examiner — Dennis J Parad(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton; Marlan D. Walker(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

US 9,114,145 B2

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(56)

References Cited**U.S. PATENT DOCUMENTS**

5,891,462 A	4/1999	Carrara	7,153,522 B1	12/2006	Ikeura et al.
5,902,603 A	5/1999	Chen et al.	7,175,850 B2	2/2007	Cevc
5,904,931 A	5/1999	Lipp et al.	7,198,800 B1	4/2007	Ko
5,906,830 A	5/1999	Farinas et al.	7,381,427 B2	6/2008	Ancira et al.
5,912,010 A	6/1999	Wille et al.	7,456,159 B2	11/2008	Houze et al.
5,919,477 A	7/1999	Bevan et al.	7,498,303 B2	3/2009	Arnold et al.
5,942,243 A	8/1999	Shah	7,534,780 B2	5/2009	Wyrwa et al.
5,952,000 A	9/1999	Venkateshwaran et al.	7,569,274 B2	8/2009	Besse et al.
5,968,919 A	10/1999	Samour et al.	7,799,769 B2	9/2010	White et al.
5,985,311 A	11/1999	Cordes et al.	7,815,936 B2	10/2010	Hasenzahl et al.
5,985,850 A	11/1999	Falk et al.	7,829,116 B2	11/2010	Griswold et al.
5,989,568 A	11/1999	Breton et al.	7,850,992 B2	12/2010	Kim et al.
6,007,835 A	12/1999	Bon Lapillonne et al.	7,854,753 B2	12/2010	Kraft et al.
6,010,715 A	1/2000	Wick et al.	7,871,643 B2	1/2011	Lizio et al.
6,013,276 A	1/2000	Math et al.	7,960,368 B2	6/2011	Nickisch et al.
6,024,974 A	2/2000	Li	8,048,017 B2	11/2011	Xu
6,030,948 A	2/2000	Mann	8,063,030 B2	11/2011	Ellman
6,040,340 A	3/2000	Chwalisz et al.	8,071,576 B2	12/2011	Coelingh Bennink et al.
6,068,853 A	5/2000	Giannos et al.	8,075,916 B2	12/2011	Song et al.
6,087,352 A	7/2000	Trout	8,075,917 B2	12/2011	Chung et al.
6,090,404 A	7/2000	Meconi et al.	8,076,317 B2	12/2011	Kulmann
6,106,848 A	8/2000	Preuilh et al.	8,080,553 B2	12/2011	Keith et al.
6,124,362 A	9/2000	Bradbury et al.	8,096,940 B2	1/2012	Josephson et al.
6,139,868 A	10/2000	Hoffmann	8,114,152 B2	2/2012	Furst
6,149,935 A	11/2000	Chiang et al.	8,114,442 B2	2/2012	Tucker et al.
6,187,323 B1	2/2001	Aiache et al.	8,119,741 B2	2/2012	Pavlin
6,217,886 B1	4/2001	Onyuksel et al.	8,124,118 B2	2/2012	Lennernaes et al.
6,225,297 B1	5/2001	Stockemann et al.	8,124,595 B2	2/2012	Boissonneault
6,228,383 B1	5/2001	Hansen et al.	8,147,561 B2	4/2012	Binmoeller
6,228,852 B1	5/2001	Shaak	8,148,546 B2	4/2012	Schuster et al.
6,242,509 B1	6/2001	Berger et al.	8,158,613 B2	4/2012	Staniforth et al.
6,245,811 B1	6/2001	Horrobin et al.	8,163,722 B2	4/2012	Savoir et al.
6,267,984 B1	7/2001	Beste et al.	8,177,449 B2	5/2012	Bayly et al.
6,274,165 B1	8/2001	Meconi et al.	8,187,615 B2	5/2012	Friedman
6,303,132 B1	10/2001	Nelson	8,195,403 B2	6/2012	Ishikawa et al.
6,303,588 B1	10/2001	Danielov	8,221,785 B2	7/2012	Chien
6,312,703 B1	11/2001	Orthofer	8,222,237 B2	7/2012	Nickisch et al.
6,328,987 B1	12/2001	Marini	8,257,724 B2	9/2012	Cromack et al.
6,344,211 B1	2/2002	Hille	8,257,725 B2	9/2012	Cromack et al.
6,372,245 B1	4/2002	Bowman et al.	8,268,352 B2	9/2012	Vaya et al.
6,420,352 B1	7/2002	Knowles	8,268,806 B2	9/2012	Labrie
6,432,438 B1	8/2002	Shukla	8,268,878 B2	9/2012	Armer et al.
6,451,300 B1	9/2002	Dunlop et al.	8,288,366 B2	10/2012	Chochinov et al.
6,465,004 B1	10/2002	Rossi Montero et al.	8,318,898 B2	11/2012	Fasel et al.
6,465,005 B1	10/2002	Biali et al.	8,324,193 B2	12/2012	Lee-Sepsick et al.
6,465,006 B1	10/2002	Zhang et al.	8,337,814 B2	12/2012	Osbakken et al.
6,495,160 B2	12/2002	Esposito et al.	8,344,007 B2	1/2013	Tang et al.
6,521,250 B2	2/2003	Meconi et al.	8,353,863 B2	1/2013	Imran
6,531,149 B1	3/2003	Kirstgen et al.	8,357,723 B2	1/2013	Satyam
6,538,039 B2	3/2003	Laurent	8,361,995 B2	1/2013	Schramm
6,548,053 B1	4/2003	Stewart et al.	8,362,091 B2	1/2013	Tamarkin et al.
6,555,131 B1	4/2003	Wolff et al.	8,372,424 B2	2/2013	Berry et al.
6,562,367 B1	5/2003	Wolff et al.	8,372,806 B2	2/2013	Boehler et al.
6,562,370 B2	5/2003	Luo et al.	8,377,482 B2	2/2013	Laurie et al.
6,562,790 B2	5/2003	Chein	8,377,994 B2	2/2013	Gray et al.
6,599,519 B1	7/2003	Seo et al.	8,394,759 B2	3/2013	Barathur et al.
6,610,674 B1	8/2003	Schreiber	8,415,332 B2	4/2013	Diliberti et al.
6,635,274 B1	10/2003	Masiz et al.	8,435,972 B2	5/2013	Stein et al.
6,638,528 B1	10/2003	Kanios	8,449,879 B2	5/2013	Laurent Applegate et al.
6,649,155 B1	11/2003	Dunlop et al.	8,450,108 B2	5/2013	Boyce
6,682,757 B1	1/2004	Wright	8,454,945 B2	6/2013	McCook et al.
6,708,822 B1	3/2004	Muni	8,455,468 B2	6/2013	Hoffman et al.
6,720,001 B2	4/2004	Chen et al.	8,461,138 B2	6/2013	Boissonneault
6,743,448 B2	6/2004	Kryger	8,476,252 B2	7/2013	Achleitner et al.
6,750,291 B2	6/2004	Kim et al.	8,481,488 B2	7/2013	Carter
6,821,524 B2	11/2004	Marini	8,486,374 B2	7/2013	Tamarkin et al.
6,911,211 B2	6/2005	Eini et al.	8,486,442 B2	7/2013	Matsushita et al.
6,960,337 B2	11/2005	Daniels et al.	8,492,368 B2	7/2013	Vanlandingham et al.
6,974,569 B2	12/2005	Dunlop et al.	8,507,467 B2	8/2013	Matsui et al.
6,995,149 B1	2/2006	Endrikat et al.	8,512,693 B2	8/2013	Capito et al.
7,004,321 B1	2/2006	Palm et al.	8,512,754 B2	8/2013	Needham
7,030,104 B2	4/2006	Gray et al.	8,518,376 B2	8/2013	Tamarkin et al.
7,094,228 B2	8/2006	Zhang et al.	8,536,159 B2	9/2013	Li et al.
7,097,853 B1	8/2006	Garbe et al.	8,540,967 B2	9/2013	Barrett et al.
7,105,573 B2	9/2006	Krajcik et al.	8,541,400 B2	9/2013	Johnsson et al.
			8,551,462 B2	10/2013	Goldstein et al.
			8,557,281 B2	10/2013	Halliday et al.
			8,568,374 B2	10/2013	De Graaff et al.
			8,591,951 B2	11/2013	Kohn et al.

US 9,114,145 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

8,613,951 B2	12/2013	Zale et al.	2005/0239747 A1	10/2005	Yang et al.
8,633,178 B2	1/2014	Bernick et al.	2005/0239758 A1	10/2005	Roby
8,633,180 B2	1/2014	Li et al.	2005/0244360 A1	11/2005	Billoni
8,636,787 B2	1/2014	Sabaria	2005/0266088 A1	12/2005	Hinrichs et al.
8,636,982 B2	1/2014	Tamarkin et al.	2005/0271597 A1	12/2005	Keith
8,653,129 B2	2/2014	Fein et al.	2005/0272685 A1	12/2005	Hung
8,658,627 B2	2/2014	Voskuhl	2006/0009428 A1	1/2006	Grubb et al.
8,663,692 B1	3/2014	Mueller et al.	2006/0034904 A1	2/2006	Weimann
8,663,703 B2	3/2014	Lerner et al.	2006/0078618 A1	4/2006	Constantinides et al.
8,664,207 B2	3/2014	Li et al.	2006/0084704 A1	4/2006	Shih et al.
8,669,293 B2	3/2014	Levy et al.	2006/0088580 A1	4/2006	Meconi et al.
8,679,552 B2	3/2014	Guthery	2006/0100180 A1	5/2006	Nubbemeyer et al.
8,697,127 B2	4/2014	Sah	2006/0121102 A1	6/2006	Chiang
8,697,710 B2	4/2014	Li et al.	2006/0165744 A1	7/2006	Jamil et al.
8,703,105 B2	4/2014	Tamarkin et al.	2006/0193789 A1	8/2006	Tamarkin et al.
8,709,385 B2	4/2014	Tamarkin et al.	2006/0233743 A1	10/2006	Kelly
8,709,451 B2	4/2014	Nam et al.	2006/0233841 A1	10/2006	Brodbeck et al.
8,715,735 B2	5/2014	Funke et al.	2006/0246122 A1	11/2006	Langguth et al.
8,721,331 B2	5/2014	Raghuprasad	2006/0247221 A1	11/2006	Coelingh Bennink et al.
8,722,021 B2	5/2014	Friedman et al.	2006/0251581 A1	11/2006	McIntyre et al.
8,734,846 B2	5/2014	Ali et al.	2006/0275218 A1	12/2006	Tamarkin et al.
8,735,381 B2	5/2014	Podolski	2006/0276414 A1	12/2006	Coelingh Bennink et al.
8,741,336 B2	6/2014	Dipierro et al.	2006/0292223 A1	12/2006	Woolfson et al.
8,741,373 B2	6/2014	Bromley et al.	2007/0009559 A1	1/2007	Li et al.
8,753,661 B2	6/2014	Steinmuller Nethl et al.	2007/0037780 A1	1/2007	Grubb et al.
8,784,882 B2	7/2014	Mattern	2007/0037782 A1	1/2007	McKenzie
2001/0009673 A1	7/2001	Lipp et al.	2007/0078091 A1	1/2007	Bracht
2001/0023261 A1	9/2001	Ryoo et al.	2007/0128263 A1	6/2007	Kleinman et al.
2001/0053383 A1	12/2001	Miranda et al.	2007/0154533 A1	7/2007	Dudley
2002/0035070 A1	3/2002	Gardlik et al.	2007/0167418 A1	7/2007	Ferguson
2002/0119174 A1	8/2002	Gardlik et al.	2007/0185068 A1	8/2007	Ferguson et al.
2002/0119198 A1	8/2002	Gao et al.	2007/0190022 A1	8/2007	Bacopoulos et al.
2002/0142017 A1	10/2002	Simonnet	2007/0196415 A1	8/2007	Chen et al.
2002/0169205 A1	11/2002	Chwalisz et al.	2007/0232574 A1	10/2007	Galey et al.
2002/0193758 A1	12/2002	Sandberg	2007/0248658 A1	10/2007	Zurdo Schroeder et al.
2002/0197286 A1	12/2002	Brandman et al.	2007/0254858 A1	11/2007	Cronk
2003/0003139 A1	1/2003	Lipp et al.	2007/0255197 A1	11/2007	Humberstone et al.
2003/0027772 A1	2/2003	Breton	2007/0287688 A1	12/2007	Chan et al.
2003/0044453 A1	3/2003	Dittgen et al.	2007/0292359 A1	12/2007	Friedman et al.
2003/0091620 A1	5/2003	Fikstad et al.	2007/0292461 A1	12/2007	Tamarkin et al.
2003/0109507 A1	6/2003	Franke et al.	2007/0292493 A1	12/2007	Briere
2003/0113268 A1	6/2003	Buenafae et al.	2007/0298089 A1	12/2007	Saeki et al.
2003/0170295 A1	9/2003	Kim et al.	2008/0026040 A1	1/2008	Farr et al.
2003/0175329 A1	9/2003	Azarnoff et al.	2008/0038219 A1	2/2008	Mosbaugh et al.
2003/0175333 A1	9/2003	Shefer et al.	2008/0039405 A1	2/2008	Langley et al.
2003/0219402 A1	11/2003	Rutter	2008/0050317 A1	2/2008	Tamarkin et al.
2003/0225047 A1	12/2003	Caubel et al.	2008/0051351 A1	2/2008	Ghisalberti
2003/0225048 A1	12/2003	Caubel et al.	2008/0063607 A1	3/2008	Tamarkin et al.
2003/0235596 A1	12/2003	Gao et al.	2008/0069779 A1	3/2008	Tamarkin et al.
2003/0236236 A1	12/2003	Chen et al.	2008/0069791 A1	3/2008	Beissert
2004/0022820 A1	2/2004	Anderson	2008/0095831 A1	4/2008	McGraw
2004/0039356 A1	2/2004	Maki et al.	2008/0138390 A1	6/2008	Hsu et al.
2004/0043043 A1	3/2004	Schlyter et al.	2008/0139392 A1	6/2008	Acosta Zara et al.
2004/0048900 A1	3/2004	Flood	2008/0153789 A1	6/2008	Dmowski et al.
2004/0087564 A1	5/2004	Wright et al.	2008/0175905 A1	7/2008	Liu et al.
2004/0092494 A9	5/2004	Dudley	2008/0175908 A1	7/2008	Liu et al.
2004/0110732 A1	6/2004	Masini Eteve et al.	2008/0206156 A1	8/2008	Cronk
2004/0138103 A1	7/2004	Patt	2008/0206159 A1	8/2008	Tamarkin et al.
2004/0146539 A1	7/2004	Gupta	2008/0214512 A1	9/2008	Seitz et al.
2004/0161435 A1	8/2004	Gupta	2008/0226698 A1	9/2008	Tang et al.
2004/0191207 A1	9/2004	Lipari et al.	2008/0227763 A1	9/2008	Lanquetin et al.
2004/0210280 A1	10/2004	Liedtke	2008/0234240 A1	9/2008	Duesterberg et al.
2004/0219124 A1	11/2004	Gupta	2008/0261931 A1	10/2008	Hedner et al.
2004/0225140 A1	11/2004	Fernandez et al.	2009/0004246 A1	1/2009	Woolfson et al.
2004/0241219 A1	12/2004	Hille et al.	2009/0010968 A1	1/2009	Allart et al.
2005/0003003 A1	1/2005	Basu et al.	2009/0011041 A1	1/2009	Musaeva et al.
2005/0014729 A1	1/2005	Pulaski	2009/0017120 A1	1/2009	Trimble et al.
2005/0020550 A1	1/2005	Morris et al.	2009/0022683 A1	1/2009	Song et al.
2005/0054991 A1	3/2005	Tobyn et al.	2009/0047357 A1	2/2009	Tomohira et al.
2005/0118244 A1	6/2005	Theobald et al.	2009/0060997 A1	3/2009	Seitz et al.
2005/0129756 A1	6/2005	Podhaisky et al.	2009/0081206 A1	3/2009	Leibovitz
2005/0152956 A1	7/2005	Dudley	2009/0093440 A1	4/2009	Murad
2005/0186141 A1	8/2005	Gonda et al.	2009/0098069 A1	4/2009	Vacca
2005/0196434 A1	9/2005	Briere	2009/0099149 A1	4/2009	Liu et al.
2005/0220900 A1	10/2005	Popp et al.	2009/0130029 A1	5/2009	Tamarkin et al.

US 9,114,145 B2

Page 4

(56)	References Cited			
U.S. PATENT DOCUMENTS				
2009/0175799 A1	7/2009 Tamarkin et al.	2012/0142645 A1	6/2012 Marx	
2009/0186081 A1	7/2009 Holm et al.	2012/0148670 A1	6/2012 Kim et al.	
2009/0197843 A1	8/2009 Notelovitz et al.	2012/0172343 A1	7/2012 Lindenthal et al.	
2009/0203658 A1	8/2009 Marx et al.	2012/0184515 A1	7/2012 Klar et al.	
2009/0227550 A1	9/2009 Mattern	2012/0231052 A1	9/2012 Sitruk Ware et al.	
2009/0285869 A1	11/2009 Trimble	2012/0232011 A1	9/2012 Kneissel et al.	
2009/0324714 A1	12/2009 Liu et al.	2012/0232042 A1	9/2012 Klar et al.	
2010/0008985 A1	1/2010 Pellikaan et al.	2012/0263679 A1	10/2012 Marlow et al.	
2010/0034838 A1	2/2010 Staniforth et al.	2012/0277249 A1	11/2012 Andersson et al.	
2010/0034880 A1	2/2010 Sintov et al.	2012/0277727 A1	11/2012 Doshi et al.	
2010/0055138 A1	3/2010 Margulies et al.	2012/0295911 A1	11/2012 Mannion et al.	
2010/0086501 A1	4/2010 Chang et al.	2012/0301517 A1	11/2012 Zhang et al.	
2010/0119585 A1	5/2010 Hille et al.	2012/0301538 A1	11/2012 Gordon Beresford et al.	
2010/0143420 A1	6/2010 Shenoy et al.	2012/0302535 A1	11/2012 Caufriez et al.	
2010/0143481 A1	6/2010 Shenoy et al.	2012/0316130 A1	12/2012 Hendrix	
2010/0150993 A1	6/2010 Theobald et al.	2012/0316496 A1	12/2012 Hoffmann et al.	
2010/0204326 A1	8/2010 D Souza	2012/0321579 A1	12/2012 Edelson et al.	
2010/0210994 A1	8/2010 Zarif	2012/0322779 A9	12/2012 Voskuhl	
2010/0221195 A1	9/2010 Tamarkin et al.	2012/0328549 A1	12/2012 Edelson et al.	
2010/0227797 A1	9/2010 Axelson et al.	2012/0329738 A1	12/2012 Liu	
2010/0247482 A1	9/2010 Cui et al.	2013/0004619 A1	1/2013 Chow et al.	
2010/0247635 A1	9/2010 Rosenberg et al.	2013/0011342 A1	1/2013 Tamarkin et al.	
2010/0273730 A1	10/2010 Hsu et al.	2013/0017239 A1	1/2013 Viladot Petit et al.	
2010/0278759 A1	11/2010 Murad	2013/0023505 A1	1/2013 Garfield et al.	
2010/0279988 A1	11/2010 Setiawan et al.	2013/0023823 A1	1/2013 Simpson et al.	
2010/0291191 A1	11/2010 Shoichet et al.	2013/0028850 A1	1/2013 Tamarkin et al.	
2010/0292199 A1	11/2010 Leverd et al.	2013/0029957 A1	1/2013 Giliyar et al.	
2010/0322884 A1	12/2010 Dipietro et al.	2013/0045266 A1	2/2013 Choi et al.	
2011/0039814 A1	2/2011 Huatan et al.	2013/0045953 A1	2/2013 Sitruk Ware et al.	
2011/0087192 A1	4/2011 Uhland et al.	2013/0059795 A1	3/2013 Lo et al.	
2011/0098258 A1	4/2011 Masini Eteve et al.	2013/0064897 A1	3/2013 Binay	
2011/0104268 A1	5/2011 Pachot et al.	2013/0072466 A1	3/2013 Choi et al.	
2011/0130372 A1	6/2011 Agostinacchio et al.	2013/0084257 A1	4/2013 Ishida et al.	
2011/0142945 A1	6/2011 Chen et al.	2013/0085123 A1	4/2013 Li et al.	
2011/0152840 A1	6/2011 Lee et al.	2013/0089574 A1	4/2013 Schmidt Gollwitzer et al.	
2011/0158920 A1	6/2011 Morley et al.	2013/0090318 A1	4/2013 Ullmann et al.	
2011/0171140 A1	7/2011 Illum et al.	2013/0102781 A1	4/2013 Bevill et al.	
2011/0190201 A1	8/2011 Hyde et al.	2013/0108551 A1	5/2013 Langereis et al.	
2011/0195031 A1	8/2011 Du	2013/0116215 A1	5/2013 Coma et al.	
2011/0238003 A1	9/2011 Bruno Raimondi et al.	2013/0116222 A1	5/2013 Arnold et al.	
2011/0244043 A1	10/2011 Xu et al.	2013/0122051 A1	5/2013 Abidi et al.	
2011/0250256 A1	10/2011 Hyun Oh et al.	2013/0123175 A1	5/2013 Hill et al.	
2011/0250259 A1	10/2011 Buckman	2013/0123220 A1	5/2013 Queiroz	
2011/0262373 A1	10/2011 Umbert Millet	2013/0123351 A1	5/2013 Dewitt	
2011/0275584 A1	11/2011 Wilckens et al.	2013/0131027 A1	5/2013 Pakkalin et al.	
2011/0281832 A1	11/2011 Li et al.	2013/0131028 A1	5/2013 Snyder et al.	
2011/0287094 A1	11/2011 Penhasi et al.	2013/0131029 A1	5/2013 Bakker et al.	
2011/0294738 A1	12/2011 Ren et al.	2013/0149314 A1	6/2013 Bullerdiek et al.	
2011/0300167 A1	12/2011 McMurry et al.	2013/0164225 A1	6/2013 Tamarkin et al.	
2011/0301087 A1	12/2011 McBride et al.	2013/0164346 A1	6/2013 Lee et al.	
2011/0306579 A1	12/2011 Stein	2013/0165744 A1	6/2013 Carson et al.	
2011/0318405 A1	12/2011 Erwin	2013/0178452 A1	7/2013 King	
2011/0318431 A1	12/2011 Gulati	2013/0183254 A1	7/2013 Zhou et al.	
2012/0021041 A1	1/2012 Rossi et al.	2013/0183325 A1	7/2013 Bottoni et al.	
2012/0028888 A1	2/2012 Janz et al.	2013/0189193 A1	7/2013 Tamarkin et al.	
2012/0028910 A1	2/2012 Combal et al.	2013/0189196 A1	7/2013 Tamarkin et al.	
2012/0028936 A1	2/2012 Gloger et al.	2013/0189230 A1	7/2013 Shoichet et al.	
2012/0046264 A1	2/2012 Simes et al.	2013/0189368 A1	7/2013 Mosqueira et al.	
2012/0046518 A1	2/2012 Yoakum et al.	2013/0210709 A1	8/2013 McMurry et al.	
2012/0058171 A1	3/2012 De Graaff et al.	2013/0216550 A1	8/2013 Penninger et al.	
2012/0058962 A1	3/2012 Cumming et al.	2013/0216596 A1	8/2013 Viladot Petit et al.	
2012/0058979 A1	3/2012 Keith et al.	2013/0224177 A1	8/2013 Kim et al.	
2012/0064135 A1	3/2012 Levin et al.	2013/0224257 A1	8/2013 Sah et al.	
2012/0065179 A1	3/2012 Andersson	2013/0224268 A1	8/2013 Alam et al.	
2012/0087872 A1	4/2012 Tamarkin et al.	2013/0224300 A1	8/2013 Maggio	
2012/0101073 A1	4/2012 Mannion et al.	2013/0225412 A1	8/2013 Sardari Lodriche et al.	
2012/0121517 A1	5/2012 Song et al.	2013/0225542 A1	8/2013 Poegh et al.	
2012/0121692 A1	5/2012 Xu et al.	2013/0226113 A1	8/2013 Schumacher et al.	
2012/0122829 A1	5/2012 Taravella et al.	2013/0243696 A1	9/2013 Wang et al.	
2012/0128654 A1	5/2012 Terpstra et al.	2013/0245253 A1	9/2013 Marx et al.	
2012/0128683 A1	5/2012 Shantha	2013/0245570 A1	9/2013 Jackson	
2012/0128733 A1	5/2012 Perrin et al.	2013/0261096 A1	10/2013 Merian et al.	
2012/0129773 A1	5/2012 Geier et al.	2013/0266645 A1	10/2013 Becker et al.	
2012/0129819 A1	5/2012 Vancaille et al.	2013/0267485 A1	10/2013 Da Silva Maia Filho	
2012/0136013 A1	5/2012 Li et al.	2013/0273167 A1	10/2013 Lee et al.	
		2013/0274211 A1	10/2013 Burman et al.	
		2013/0280213 A1	10/2013 Voskuhl	
		2013/0316374 A1	11/2013 Penninger et al.	
		2013/0317065 A1	11/2013 Tatani et al.	

US 9,114,145 B2

Page 5

(56)

References Cited

U.S. PATENT DOCUMENTS

2013/0317315	A1	11/2013	Lu et al.
2013/0324565	A1	12/2013	Li et al.
2013/0331363	A1	12/2013	Li et al.
2013/0338124	A1	12/2013	Li et al.
2013/0345187	A1	12/2013	Rodriguez Oquendo
2014/0018335	A1	1/2014	Tatani et al.
2014/0024590	A1	1/2014	Weidhaas et al.
2014/0031289	A1	1/2014	Song et al.
2014/0031323	A1	1/2014	Perez
2014/0066416	A1	3/2014	Leunis et al.
2014/0072531	A1	3/2014	Kim et al.
2014/0079686	A1	3/2014	Barman et al.
2014/0088058	A1	3/2014	Maurizio
2014/0088059	A1	3/2014	Perumal et al.
2014/0094426	A1	4/2014	Drummond et al.
2014/0100159	A1	4/2014	Conrad
2014/0100206	A1	4/2014	Bernick et al.
2014/0113889	A1	4/2014	Connor et al.
2014/0127185	A1	5/2014	Stein et al.
2014/0127280	A1	5/2014	Duesterberg et al.
2014/0127308	A1	5/2014	Opara et al.
2014/0128798	A1	5/2014	Janson et al.
2014/0148491	A1	5/2014	Valia et al.
2014/0186332	A1	7/2014	Ezrin et al.
2014/0187487	A1	7/2014	Shoichet et al.
2014/0193523	A1	7/2014	Henry
2014/0194396	A1	7/2014	Li et al.
2014/0206616	A1	7/2014	Ko et al.

FOREIGN PATENT DOCUMENTS

WO	WO2012098090	A1	7/2012
WO	WO2012116277	A1	8/2012
WO	WO2012118563	A2	9/2012
WO	WO2012120365	A1	9/2012
WO	WO2012127501	A2	9/2012
WO	WO2012156561	A1	11/2012
WO	WO2012156822	A1	11/2012
WO	WO2012158483	A2	11/2012
WO	WO2012166909	A1	12/2012
WO	WO2012170578	A1	12/2012
WO	WO2013011501	A1	1/2013
WO	WO2013025449	A1	2/2013
WO	WO2013028639	A1	2/2013
WO	WO2013035101	A1	3/2013
WO	WO2013044067	A1	3/2013
WO	WO2013045404	A2	4/2013
WO	WO2013059285	A1	4/2013
WO	WO2013063279	A1	5/2013
WO	WO2013064620	A1	5/2013
WO	WO2013071281	A1	5/2013
WO	WO2013088254		6/2013
WO	WO2013102665	A1	7/2013
WO	WO2013106437	A1	7/2013
WO	WO2013113690		8/2013
WO	WO2013124415	A1	8/2013
WO	WO2013127727	A1	9/2013
WO	WO2013127728	A1	9/2013

WO	WO2013144356	A1	10/2013
WO	WO2013149258	A2	10/2013
WO	WO2013158424	A2	10/2013
WO	WO2013158454	A2	10/2013
WO	WO2013170052	A1	11/2013
WO	WO2013178587	A1	12/2013
WO	WO2013181449	A1	12/2013
WO	WO2014001904	A1	1/2014
WO	WO2014004424	A1	1/2014
WO	WO2014009434	A1	1/2014
WO	WO2014018569	A1	1/2014
WO	WO2014018570	A1	1/2014
WO	WO2014018571	A2	1/2014
WO	WO2014018856	A1	1/2014
WO	WO2014018932	A2	1/2014
WO	WO2014031958	A1	2/2014
WO	WO2014041120	A1	3/2014
WO	WO2014052792	A1	4/2014
WO	WO2014056897	A1	4/2014
WO	WO2014066442	A2	5/2014
WO	WO2014074846	A1	5/2014
WO	WO2014076231	A1	5/2014
WO	WO2014076569	A2	5/2014
WO	WO2014081598	A1	5/2014
WO	WO2014086739	A1	6/2014
WO	WO2014093114	A1	6/2014
WO	WO2014104784	A1	7/2014

OTHER PUBLICATIONS

- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
- Gattefossé Sas, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé Sas, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé Sas, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.

* cited by examiner

U.S. Patent

Aug. 25, 2015

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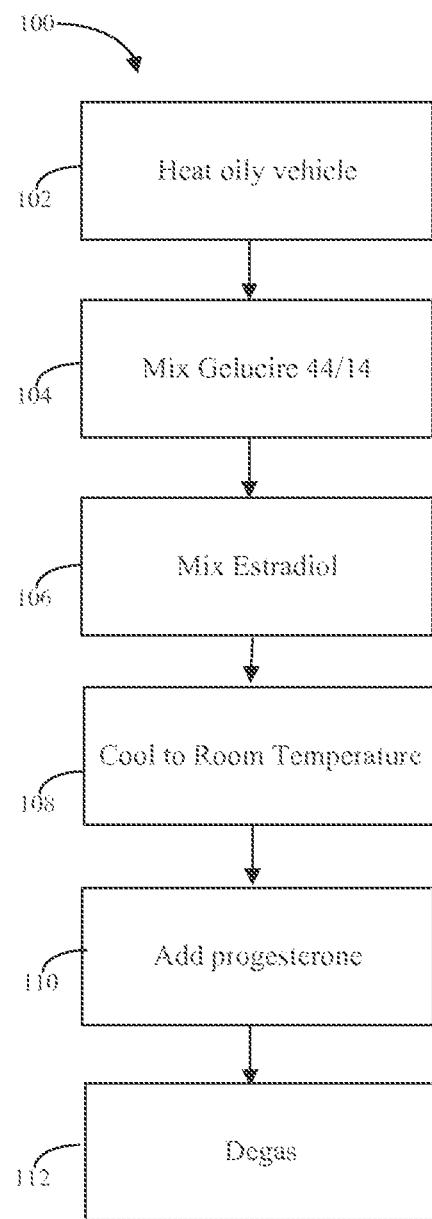
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Fig. 1

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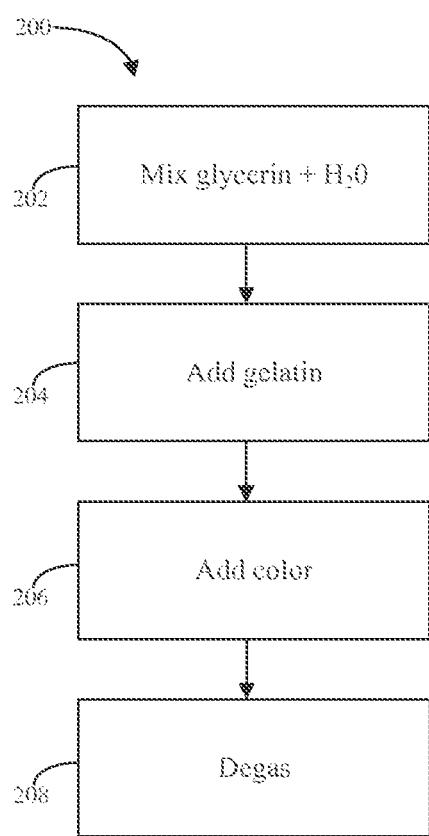


Fig. 2

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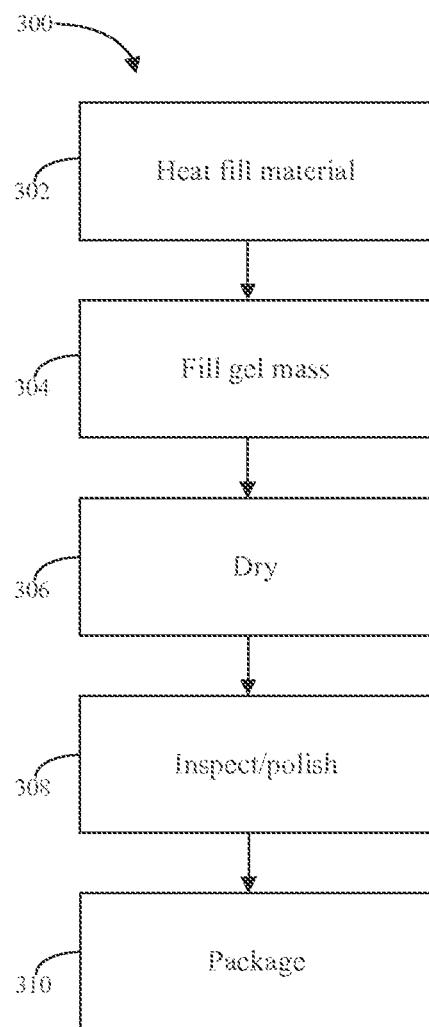


Fig. 3

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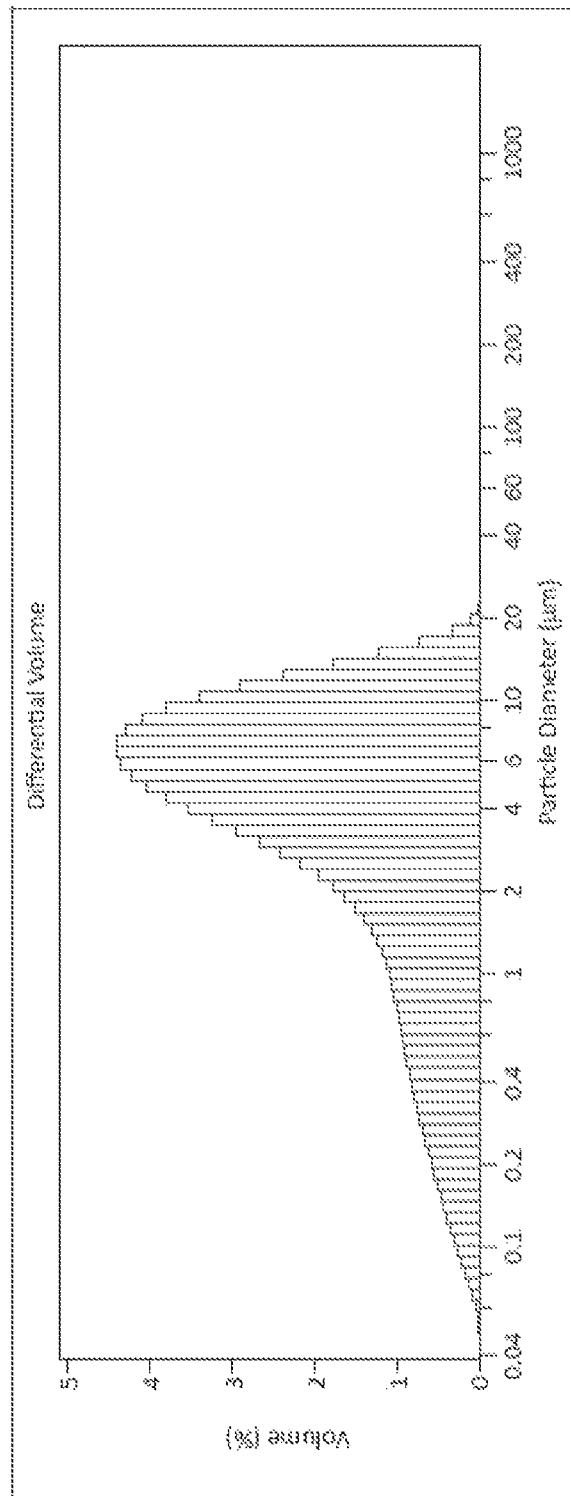


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCES TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which application claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

35 SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via 40 pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, 45 each in accordance with the invention are set forth below.

50 BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated 55 herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in 65 accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. DEFINITIONS

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pk) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, Tmax.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

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The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. DESCRIPTION AND PREFERRED EMBODIMENTS

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/500 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to

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about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from

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about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others.

Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μ m to 2000 μ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

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Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

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In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

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In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

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Example 1

Estradiol Solubility

5 In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

10 Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

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TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

30 It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

35 Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with 40 various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

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Example 3

65 Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold

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cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Myglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF	82.57	577.97	
Gelucire 44/14, NF	10.0	70.00	
TOTAL	100.00	700.00	

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/-2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

20 In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
35 Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

40 In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Cap- sule (mg)	% w/w	Qty/Cap- sule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/di- glycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
55 Lauroyl polyoxy-32- glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00	100		6.0 kg

60 For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is

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removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxy1-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

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TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
10	1. Progesterone, USP, micronized	50.00	7.14	50.00	0.50
	2. Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
	3. Capmul MCM, NF	82.57	577.97	5.78	
	4. Gelucire 44/14, NF	10.0	70.00	0.70	
			Total:	100.00	700.00
					7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
35	1. Progesterone, USP, micronized	50.00	25.000	50.00	500.00
	2. Estradiol Hemihydrate	0.25	0.129	0.26	2.58
	3. Capmul MCM, NF	73.371	146.74	146.742	
	4. Gelucire 44/14, NF	1.500	3.00	3.00	30.00
			Total:	100.000	200.00 mg 2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
55	1. Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
	2. Estradiol Hemihydrate	2.00	0.35	2.07	20.7
	3. Capmul MCM, NF	65.32	391.93	3919.3	
	4. Gelucire 44/14, NF	1.00	6.0	6.0	60.0
			Total:	100.00	600.0 mg 6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until

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dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condi-

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tion, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70°C.±20°C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+-3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+-10° C. The wedge temperature may be 38° C.+-3° C. The drum cooling temperature may be 4° C.+-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A method of treating a menopause-related symptom in a woman comprising: administering to the woman an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent;

wherein each of the estradiol and the suspended progestrone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;

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wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and
wherein the solubilizing agent comprises an effective amount at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

5 2. The method of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

10 3. The method of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The method of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

15 5. The method of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

20 6. The method of claim 1, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

25 7. A method of treating a menopause symptom in a woman comprising: administering a pharmaceutical composition to the woman, the pharmaceutical composition comprising:

solubilized estradiol;
suspended progesterone; and
a solubilizing agent, the solubilizing agent comprising an effective amount mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid;

30 wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and
wherein the estradiol does not precipitate for at least 14 days.

35 8. The method of claim 7, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

40 9. The method of claim 7, wherein the formulation is formulated as a gelatin capsule.

10. The method of claim 7, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

45 11. The method of claim 7, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

50 12. The method of claim 7, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

13. A method of treating a menopause symptom comprising: administering an effective amount of a pharmaceutical composition to a woman, the pharmaceutical composition comprising:

55 solubilized estradiol;
suspended progesterone; and
a solubilizing agent, the estradiol being stable in the solubilizing agent for at least 14 days;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent;

wherein the estradiol and progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent, and

wherein the solubilizing agent comprises an effective amount mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

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14. The method of claim **13**, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

15. The method of claim **13**, wherein the formulation is formulated as a gelatin capsule. 5

16. The method of claim **13**, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

17. The method of claim **13**, wherein the ratio of progestrone to estradiol is about 24:1, about 25:1, about 96:1, about 10 100:1, about 192:1, or about 200:1.

18. The method of claim **13**, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

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CERTIFICATE OF CORRECTION

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APPLICATION NO. : 14/475946
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INVENTOR(S) : Brian A. Bernick et al.

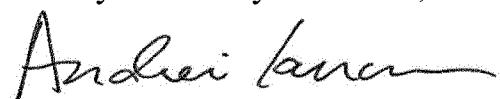
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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT I



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(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 9,114,146 B2
(45) **Date of Patent:** *Aug. 25, 2015

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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This patent is subject to a terminal disclaimer.

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(51) **Int. Cl.**

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A61K 31/57 (2006.01)
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A61K 31/565 (2006.01)
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CPC : *A61K 31/57* (2013.01); *A61K 9/16* (2013.01);
A61K 9/4858 (2013.01); *A61K 9/7023* (2013.01); *A61K 31/565* (2013.01)

(58) **Field of Classification Search**

USPC 514/169; 424/452
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,232,438 A	2/1941	Butenandt
5,538,736 A	7/1996	Hoffmann et al.
5,556,635 A	9/1996	Istin et al.
5,580,572 A	12/1996	Mikler et al.

5,605,702 A	2/1997	Teillaud et al.
5,607,691 A	3/1997	Hale et al.
5,607,693 A	3/1997	Bonte et al.
5,609,617 A	3/1997	Shealy et al.
5,626,866 A	5/1997	Ebert et al.
5,653,983 A	8/1997	Meybeck et al.
5,660,839 A	8/1997	Allec et al.
5,662,927 A	9/1997	Ehrlich et al.
5,663,160 A	9/1997	Meybeck et al.
5,686,097 A	11/1997	Taskovich et al.
5,693,335 A	12/1997	Xia et al.
5,700,480 A	12/1997	Hille et al.
5,719,197 A	2/1998	Kanios et al.
5,770,220 A	6/1998	Meconi et al.
5,770,227 A	6/1998	Dong et al.
5,780,044 A	7/1998	Yewey et al.
5,780,050 A	7/1998	Jain et al.
5,788,984 A	8/1998	Guenther et al.
5,820,878 A	10/1998	Hirano et al.
5,840,327 A	11/1998	Gale et al.
5,843,468 A	12/1998	Burkoth et al.
5,843,979 A	12/1998	Wille et al.
5,858,394 A	1/1999	Lipp et al.
5,863,552 A	1/1999	Yue
5,882,676 A	3/1999	Lee et al.
5,885,612 A	3/1999	Meconi et al.
5,888,533 A	3/1999	Dunn
5,891,462 A	4/1999	Carrara

(Continued)

FOREIGN PATENT DOCUMENTS

WO	WO9619975	7/1996
WO	WO0241878	5/2002

(Continued)

OTHER PUBLICATIONS

Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.

Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.

Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.

Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.

(Continued)

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(74) **Attorney, Agent, or Firm** — Kilpatrick Townsend & Stockton; Marlan D. Walker

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

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(56)

References Cited**U.S. PATENT DOCUMENTS**

5,902,603 A	5/1999	Chen et al.	7,153,522 B1	12/2006	Ikeura et al.
5,904,931 A	5/1999	Lipp et al.	7,175,850 B2	2/2007	Cevc
5,906,830 A	5/1999	Farinas et al.	7,198,800 B1	4/2007	Ko
5,912,010 A	6/1999	Wille et al.	7,381,427 B2	6/2008	Ancira et al.
5,919,477 A	7/1999	Bevan et al.	7,456,159 B2	11/2008	Houze et al.
5,942,243 A	8/1999	Shah	7,498,303 B2	3/2009	Arnold et al.
5,942,531 A	8/1999	Diaz et al.	7,534,780 B2	5/2009	Wyrwa et al.
5,952,000 A	9/1999	Venkateshwaran et al.	7,569,274 B2	8/2009	Besse et al.
5,968,919 A	10/1999	Samour et al.	7,799,769 B2	9/2010	White et al.
5,985,311 A	11/1999	Cordes et al.	7,815,936 B2	10/2010	Hasenzahl et al.
5,985,850 A	11/1999	Falk et al.	7,829,116 B2	11/2010	Griswold et al.
5,989,568 A	11/1999	Breton et al.	7,850,992 B2	12/2010	Kim et al.
6,007,835 A	12/1999	Bon Lapillonne et al.	7,854,753 B2	12/2010	Kraft et al.
6,010,715 A	1/2000	Wick et al.	7,871,643 B2	1/2011	Lizio et al.
6,013,276 A	1/2000	Math et al.	7,925,519 B2	4/2011	Greene
6,024,974 A	2/2000	Li	7,945,459 B2	5/2011	Grace et al.
6,030,948 A	2/2000	Mann	7,960,368 B2	6/2011	Nickisch et al.
6,040,340 A	3/2000	Chwalisz et al.	8,048,017 B2	11/2011	Xu
6,068,853 A	5/2000	Giannos et al.	8,063,030 B2	11/2011	Ellman
6,087,352 A	7/2000	Trout	8,075,916 B2	12/2011	Coelingh Bennink et al.
6,090,404 A	7/2000	Meconi et al.	8,075,917 B2	12/2011	Song et al.
6,106,848 A	8/2000	Preuilh et al.	8,076,317 B2	12/2011	Chung et al.
6,124,362 A	9/2000	Bradbury et al.	8,080,553 B2	12/2011	Kulmann
6,139,868 A	10/2000	Hoffmann	8,096,940 B2	1/2012	Keith et al.
6,149,935 A	11/2000	Chiang et al.	8,114,152 B2	2/2012	Furst
6,187,323 B1	2/2001	Aiache et al.	8,114,442 B2	2/2012	Tucker et al.
6,217,886 B1	4/2001	Onyueksel et al.	8,119,741 B2	2/2012	Pavlin
6,225,297 B1	5/2001	Stockemann et al.	8,121,886 B2	2/2012	Azar
6,228,383 B1	5/2001	Hansen et al.	8,124,118 B2	2/2012	Lennernaes et al.
6,228,852 B1	5/2001	Shaak	8,124,595 B2	2/2012	Boissonneault
6,242,509 B1	6/2001	Berger et al.	8,147,561 B2	4/2012	Binmoeller
6,245,811 B1	6/2001	Horrobin et al.	8,148,546 B2	4/2012	Schuster et al.
6,267,984 B1	7/2001	Beste et al.	8,158,613 B2	4/2012	Staniforth et al.
6,274,165 B1	8/2001	Meconi et al.	8,163,722 B2	4/2012	Savoir et al.
6,303,132 B1	10/2001	Nelson	8,177,449 B2	5/2012	Bayly et al.
6,303,588 B1	10/2001	Danielov	8,187,615 B2	5/2012	Friedman
6,312,703 B1	11/2001	Orthofer	8,195,403 B2	6/2012	Ishikawa et al.
6,328,987 B1	12/2001	Marini	8,221,785 B2	7/2012	Chien
6,344,211 B1	2/2002	Hille	8,222,237 B2	7/2012	Nickisch et al.
6,372,245 B1	4/2002	Bowman et al.	8,257,724 B2	9/2012	Cromack et al.
6,420,352 B1	7/2002	Knowles	8,257,725 B2	9/2012	Cromack et al.
6,432,438 B1	8/2002	Shukla	8,268,352 B2	9/2012	Vaya et al.
6,451,300 B1	9/2002	Dunlop et al.	8,268,806 B2	9/2012	Labrie
6,465,004 B1	10/2002	Rossi Montero et al.	8,288,366 B2	9/2012	Armer et al.
6,465,005 B1	10/2002	Biali et al.	8,318,898 B2	10/2012	Chochinov et al.
6,465,006 B1	10/2002	Zhang et al.	8,324,193 B2	11/2012	Fasel et al.
6,495,160 B2	12/2002	Esposito et al.	8,337,814 B2	12/2012	Lee Sepsick et al.
6,521,250 B2	2/2003	Meconi et al.	8,344,007 B2	12/2012	Osbakken et al.
6,531,149 B1	3/2003	Kirstgen et al.	8,353,863 B2	1/2013	Tang et al.
6,538,039 B2	3/2003	Laurent	8,357,723 B2	1/2013	Imran
6,548,053 B1	4/2003	Stewart et al.	8,361,995 B2	1/2013	Satyam
6,555,131 B1	4/2003	Wolff et al.	8,362,091 B2	1/2013	Schramm
6,562,367 B1	5/2003	Wolff et al.	8,372,424 B2	1/2013	Tamarkin et al.
6,562,370 B2	5/2003	Luo et al.	8,372,806 B2	2/2013	Berry et al.
6,562,790 B2	5/2003	Chein	8,377,482 B2	2/2013	Boehler et al.
6,599,519 B1	7/2003	Seo et al.	8,377,994 B2	2/2013	Laurie et al.
6,610,674 B1	8/2003	Schreiber	8,394,759 B2	2/2013	Gray et al.
6,635,274 B1	10/2003	Masiz et al.	8,415,332 B2	3/2013	Barathur et al.
6,638,528 B1	10/2003	Kanios	8,435,972 B2	4/2013	Diliberti et al.
6,649,155 B1	11/2003	Dunlop et al.	8,449,879 B2	5/2013	Stein et al.
6,682,757 B1	1/2004	Wright	8,450,108 B2	5/2013	Laurent Applegate et al.
6,708,822 B1	3/2004	Muni	8,454,945 B2	5/2013	Boyce
6,720,001 B2	4/2004	Chen et al.	8,455,468 B2	6/2013	Mccook et al.
6,743,448 B2	6/2004	Kryger	8,461,138 B2	6/2013	Hoffman et al.
6,750,291 B2	6/2004	Kim et al.	8,476,252 B2	6/2013	Boissonneault
6,821,524 B2	11/2004	Marini	8,486,374 B2	7/2013	Achleitner et al.
6,911,211 B2	6/2005	Eini et al.	8,486,442 B2	7/2013	Tamarkin et al.
6,960,337 B2	11/2005	Daniels et al.	8,492,368 B2	7/2013	Matsui et al.
6,974,569 B2	12/2005	Dunlop et al.	8,507,467 B2	8/2013	Capito et al.
6,995,149 B1	2/2006	Endrikat et al.	8,512,693 B2	8/2013	Needham
7,004,321 B1	2/2006	Palm et al.	8,512,754 B2	8/2013	Tamarkin et al.
7,030,104 B2	4/2006	Gray et al.	8,518,376 B2	8/2013	Li et al.
7,094,228 B2	8/2006	Zhang et al.	8,536,159 B2	9/2013	Barrett et al.
7,097,853 B1	8/2006	Garbe et al.	8,540,967 B2	9/2013	Goldstein et al.
7,105,573 B2	9/2006	Krajcik et al.	8,541,400 B2	9/2013	Johnsson et al.
			8,551,462 B2	10/2013	

US 9,114,146 B2

Page 3

References Cited			
U.S. PATENT DOCUMENTS			
8,557,281 B2	10/2013	Halliday et al.	2004/0161435 A1
8,568,374 B2	10/2013	De Graaff et al.	2004/0191207 A1
8,591,951 B2	11/2013	Kohn et al.	2004/0210280 A1
8,613,951 B2	12/2013	Zale et al.	2004/0219124 A1
8,633,178 B2	1/2014	Bernick et al.	2004/0225140 A1
8,633,180 B2	1/2014	Li et al.	2004/0241219 A1
8,636,787 B2	1/2014	Sabaria	2004/0243437 A1
8,636,982 B2	1/2014	Tamarkin et al.	2005/0003003 A1
8,653,129 B2	2/2014	Fein et al.	2005/0014729 A1
8,658,627 B2	2/2014	Voskuhl	2005/0020550 A1
8,663,692 B1	3/2014	Mueller et al.	2005/0054991 A1
8,663,703 B2	3/2014	Lerner et al.	2005/0118244 A1
8,664,207 B2	3/2014	Li et al.	2005/0129756 A1
8,669,293 B2	3/2014	Levy et al.	2005/0152956 A1
8,679,552 B2	3/2014	Guthery	2005/0186141 A1
8,694,358 B2	4/2014	Tryfon	2005/0239747 A1
8,697,127 B2	4/2014	Sah	2005/0239758 A1
8,697,710 B2	4/2014	Li et al.	2005/0244360 A1
8,703,105 B2	4/2014	Tamarkin et al.	2005/0266088 A1
8,709,385 B2	4/2014	Tamarkin et al.	2005/0271597 A1
8,709,451 B2	4/2014	Nam et al.	2005/0272685 A1
8,715,735 B2	5/2014	Funke et al.	2006/0009428 A1
8,721,331 B2	5/2014	Raghuprasad	2006/0034904 A1
8,722,021 B2	5/2014	Friedman et al.	2006/0040904 A1
8,734,846 B2	5/2014	Ali et al.	2006/0078618 A1
8,735,381 B2	5/2014	Podolski	2006/0084704 A1
8,741,336 B2	6/2014	Dipierro et al.	2006/0088580 A1
8,741,373 B2	6/2014	Bromley et al.	2006/0100180 A1
8,753,661 B2	6/2014	Steinmueller Nethl et al.	2006/0121102 A1
8,784,882 B2	7/2014	Mattern	2006/0165744 A1
8,846,648 B2	9/2014	Bernick et al.	2006/0193789 A1
8,846,649 B2	9/2014	Bernick et al.	2006/0233743 A1
8,933,059 B2	1/2015	Bernick et al.	2006/0233841 A1
8,987,237 B2	3/2015	Bernick et al.	2006/0246122 A1
8,987,238 B2	3/2015	Bernick et al.	2006/0247221 A1
8,993,548 B2	3/2015	Bernick et al.	2006/0251581 A1
8,993,549 B2	3/2015	Bernick et al.	2006/0275218 A1
9,006,222 B2	4/2015	Bernick et al.	2006/0276414 A1
9,012,434 B2	4/2015	Bernick et al.	2006/0292223 A1
2001/0009673 A1	7/2001	Lipp et al.	2007/0009559 A1
2001/0023261 A1	9/2001	Ryoo et al.	2007/0009594 A1
2001/0032125 A1	10/2001	Bhan et al.	2007/0010550 A1
2001/0053383 A1	12/2001	Miranda et al.	2007/0014839 A1
2002/0035070 A1	3/2002	Gardlik et al.	2007/0015698 A1
2002/0119174 A1	8/2002	Gardlik et al.	2007/0037780 A1
2002/0119198 A1	8/2002	Gao et al.	2007/0037782 A1
2002/0142017 A1	10/2002	Simonnet	2007/0078091 A1
2002/0169205 A1	11/2002	Chwalisz et al.	2007/0128263 A1
2002/0193758 A1	12/2002	Sandberg	2007/0154533 A1
2002/0197286 A1	12/2002	Brandman et al.	2007/0167418 A1
2003/0003139 A1	1/2003	Lipp et al.	2007/0185068 A1
2003/0027772 A1	2/2003	Breton	2007/0190022 A1
2003/0044453 A1	3/2003	Dittgen et al.	2007/0196415 A1
2003/0077297 A1*	4/2003	Chen et al. 424/400	2007/0232574 A1
2003/0091620 A1	5/2003	Fikstad et al.	2007/0248658 A1
2003/0109507 A1	6/2003	Franke et al.	2007/0254585 A1
2003/0113268 A1	6/2003	Buenafae et al.	2007/0255197 A1
2003/0170295 A1	9/2003	Kim et al.	2007/0287688 A1
2003/0175329 A1	9/2003	Azarnoff et al.	2007/0292359 A1
2003/0175333 A1	9/2003	Shefer et al.	2007/0292461 A1
2003/0219402 A1	11/2003	Rutter	2007/0292493 A1
2003/0225047 A1	12/2003	Caubel et al.	2007/0298089 A1
2003/0225048 A1	12/2003	Caubel et al.	2008/0026040 A1
2003/0235596 A1	12/2003	Gao et al.	2008/0038219 A1
2003/0236236 A1	12/2003	Chen et al.	2008/0039405 A1
2004/0022820 A1	2/2004	Anderson	2008/0050317 A1
2004/0039356 A1	2/2004	Maki et al.	2008/0051351 A1
2004/0043043 A1	3/2004	Schlyter et al.	2008/0063607 A1
2004/0048900 A1	3/2004	Flood	2008/0069779 A1
2004/0087564 A1	5/2004	Wright et al.	2008/0069791 A1
2004/0092494 A9	5/2004	Dudley	2008/0095831 A1
2004/0093261 A1	5/2004	Jain et al.	2008/0138390 A1
2004/0110732 A1	6/2004	Masini Eteve et al.	2008/0139392 A1
2004/0138103 A1	7/2004	Patt	2008/0153789 A1
2004/0146539 A1	7/2004	Gupta	2008/0175905 A1
			8/2004 Gupta
			9/2004 Lipari et al.
			10/2004 Liedtke
			11/2004 Gupta
			11/2004 Fernandez et al.
			12/2004 Hille et al.
			12/2004 Grace et al.
			1/2005 Basu et al.
			1/2005 Pulaski
			1/2005 Morris et al.
			3/2005 Tobyn et al.
			6/2005 Theobald et al.
			6/2005 Podhaisky et al.
			7/2005 Dudley
			8/2005 Gonda et al.
			9/2005 Brierre
			10/2005 Popp et al.
			10/2005 Hodgdon
			10/2005 Austin
			10/2005 Yang et al.
			10/2005 Roby
			11/2005 Billoni
			12/2005 Hinrichs et al.
			12/2005 Keith
			12/2005 Hung
			1/2006 Grubb et al.
			2/2006 Weimann
			2/2006 Ahmed et al.
			4/2006 Constantiades et al.
			4/2006 Shih et al.
			4/2006 Meconi et al.
			5/2006 Nubbemeyer et al.
			6/2006 Chiang
			7/2006 Jamil et al.
			8/2006 Tamarkin et al.
			10/2006 Kelly
			10/2006 Brodbeck et al.
			11/2006 Langguth et al.
			11/2006 Coelingh Bennink et al.
			11/2006 McIntyre et al.
			12/2006 Tamarkin et al.
			12/2006 Coelingh Bennink et al.
			12/2006 Woolfson et al.
			1/2007 Li et al.
			1/2007 Grubb et al.
			1/2007 McKenzie
			1/2007 Bracht
			1/2007 Kleinman et al.
			2/2007 Ebert et al.
			2/2007 Hibino et al.
			4/2007 Hubler et al.
			6/2007 Gargiulo et al.
			7/2007 Dudley
			7/2007 Ferguson
			8/2007 Ferguson et al.
			8/2007 Bacopoulos et al.
			8/2007 Chen et al.
			10/2007 Galey et al.
			10/2007 Zurdo Schroeder et al.
			11/2007 Cronk
			11/2007 Humberstone et al.
			12/2007 Chan et al.
			12/2007 Friedman et al.
			12/2007 Tamarkin et al.
			12/2007 Brierre
			12/2007 Saeki et al.
			1/2008 Farr et al.
			2/2008 Mosbaugh et al.
			2/2008 Langley et al.
			2/2008 Tamarkin et al.
			2/2008 Ghisalberti
			3/2008 Tamarkin et al.
			3/2008 Tamarkin et al.
			4/2008 McGraw
			6/2008 Hsu et al.
			6/2008 Acosta Zara et al.
			6/2008 Dmowski et al.
			7/2008 Liu et al.

US 9,114,146 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2008/0175908 A1	7/2008	Liu et al.	2012/0021041 A1	1/2012	Rossi et al.	
2008/0206156 A1	8/2008	Cronk	2012/0028888 A1	2/2012	Janz et al.	
2008/0206159 A1	8/2008	Tamarkin et al.	2012/0028910 A1	2/2012	Combal et al.	
2008/0214512 A1	9/2008	Seitz et al.	2012/0028936 A1	2/2012	Gloge et al.	
2008/0226698 A1	9/2008	Tang et al.	2012/0046264 A1	2/2012	Simes et al.	
2008/0227763 A1	9/2008	Lanquette et al.	2012/0046518 A1	2/2012	Yoakum et al.	
2008/0234240 A1	9/2008	Duesterberg et al.	2012/0058171 A1	3/2012	De Graaff et al.	
2008/0261931 A1	10/2008	Hedner et al.	2012/0058962 A1	3/2012	Cumming et al.	
2009/0004246 A1	1/2009	Woolfson et al.	2012/0058979 A1	3/2012	Keith et al.	
2009/0010968 A1	1/2009	Allart et al.	2012/0064135 A1	3/2012	Levin et al.	
2009/0011041 A1	1/2009	Musaeva et al.	2012/0065179 A1	3/2012	Andersson	
2009/0017120 A1	1/2009	Trimble et al.	2012/0065221 A1	3/2012	Babul	
2009/0022683 A1	1/2009	Song et al.	2012/0087872 A1	4/2012	Tamarkin et al.	
2009/0047357 A1	2/2009	Tomohira et al.	2012/0101073 A1	4/2012	Mannion et al.	
2009/0060997 A1	3/2009	Seitz et al.	2012/0121517 A1	5/2012	Song et al.	
2009/0081206 A1	3/2009	Leibovitz	2012/0121692 A1	5/2012	Xu et al.	
2009/0093440 A1	4/2009	Murad	2012/0122829 A1	5/2012	Taravella et al.	
2009/0098069 A1	4/2009	Vacca	2012/0128654 A1	5/2012	Terpstra et al.	
2009/0099149 A1	4/2009	Liu et al.	2012/0128683 A1	5/2012	Shantha	
2009/0130029 A1	5/2009	Tamarkin et al.	2012/0128733 A1	5/2012	Perrin et al.	
2009/0164341 A1	6/2009	Sunvold et al.	2012/0129773 A1	5/2012	Geier et al.	
2009/0175799 A1	7/2009	Tamarkin et al.	2012/0172343 A1	7/2012	Vancaillie et al.	
2009/0186081 A1	7/2009	Holm et al.	2012/0184515 A1	7/2012	Marx	
2009/0197843 A1	8/2009	Notelovitz et al.	2012/0231052 A1	9/2012	Klar et al.	
2009/0203658 A1	8/2009	Marx et al.	2012/0232011 A1	9/2012	Zhang et al.	
2009/0227550 A1	9/2009	Mattern	2012/0232042 A1	9/2012	Edelson et al.	
2009/0285869 A1	11/2009	Trimble	2012/0263679 A1	10/2012	Marlow et al.	
2009/0324714 A1	12/2009	Liu et al.	2012/0277249 A1	11/2012	Andersson et al.	
2010/0008985 A1	1/2010	Pellikaan et al.	2012/0277727 A1	11/2012	Doshi et al.	
2010/0034838 A1	2/2010	Staniforth et al.	2012/0295911 A1	11/2012	Mannion et al.	
2010/0034880 A1	2/2010	Sintov et al.	2012/0301517 A1	11/2012	Zhang et al.	
2010/0055138 A1	3/2010	Margulies et al.	2012/0301538 A1	11/2012	Gordon Beresford et al.	
2010/0086501 A1	4/2010	Chang et al.	2012/0302535 A1	11/2012	Caufriez et al.	
2010/0119585 A1	5/2010	Hille et al.	2012/0316130 A1	12/2012	Hendrix	
2010/0143420 A1	6/2010	Shenoy et al.	2012/0316496 A1	12/2012	Hoffmann et al.	
2010/0143481 A1	6/2010	Shenoy et al.	2012/0321579 A1	12/2012	Edelson et al.	
2010/0150993 A1	6/2010	Theobald et al.	2012/0322779 A9	12/2012	Voskuhl	
2010/0204326 A1	8/2010	D Souza	2012/0328549 A1	12/2012	Liu	
2010/0210994 A1	8/2010	Zarif	2012/0329738 A1	12/2012	Chow et al.	
2010/0221195 A1	9/2010	Tamarkin et al.	2013/0004619 A1	1/2013	Tamarkin et al.	
2010/0227797 A1	9/2010	Axelson et al.	2013/0011342 A1	1/2013	Viladot Petit et al.	
2010/0247482 A1	9/2010	Cui et al.	2013/0017239 A1	1/2013	Garfield et al.	
2010/0247635 A1	9/2010	Rosenberg et al.	2013/0023505 A1	1/2013	Simpson et al.	
2010/0273730 A1	10/2010	Hsu et al.	2013/0023823 A1	1/2013	Agostinacchio et al.	
2010/0278759 A1	11/2010	Murad	2013/0028850 A1	1/2013	Langereis et al.	
2010/0279988 A1	11/2010	Setiawan et al.	2013/0029957 A1	1/2013	Comba et al.	
2010/0291191 A1	11/2010	Shoichet et al.	2013/0045266 A1	2/2013	Lo et al.	
2010/0292199 A1	11/2010	Leverd et al.	2013/0045953 A1	2/2013	Binay	
2010/0322884 A1	12/2010	Dipietro et al.	2013/0059795 A1	3/2013	Choi et al.	
2011/0039814 A1	2/2011	Huatan et al.	2013/0064897 A1	3/2013	Bevill et al.	
2011/0066473 A1	3/2011	Bernick et al.	2013/0072466 A1	4/2013	Ullmann et al.	
2011/0087192 A1	4/2011	Uhland et al.	2013/0084257 A1	4/2013	Ishida et al.	
2011/0098258 A1	4/2011	Masini Eteve et al.	2013/0085123 A1	4/2013	Lee et al.	
2011/0104268 A1	5/2011	Pachot et al.	2013/0089574 A1	4/2013	Schmidt Gollwitzer et al.	
2011/0130372 A1	6/2011	Agostinacchio et al.	2013/0090318 A1	4/2013	Arnold et al.	
2011/0142945 A1	6/2011	Chen et al.	2013/0102781 A1	4/2013	Abidi et al.	
2011/0152840 A1	6/2011	Lee et al.	2013/0108551 A1	5/2013	Hill et al.	
2011/0158920 A1	6/2011	Morley et al.	2013/0116215 A1	5/2013	Queiroz	
2011/0171140 A1	7/2011	Illum et al.	2013/0116222 A1	5/2013	Dewitt	
2011/0190201 A1	8/2011	Hyde et al.	2013/0122051 A1	5/2013	Bakker et al.	
2011/0195031 A1	8/2011	Du	2013/0123175 A1	5/2013	Bullerdiek et al.	
2011/0238003 A1	9/2011	Bruno Raimondi et al.	2013/0123220 A1	5/2013	Tamarkin et al.	
2011/0244043 A1	10/2011	Xu et al.	2013/0123351 A1	5/2013	Pakkalin et al.	
2011/0250256 A1	10/2011	Hyun Oh et al.	2013/0131027 A1	5/2013	Snyder et al.	
2011/0250259 A1	10/2011	Buckman	2013/0131028 A1	5/2013	Lee et al.	
2011/0262373 A1	10/2011	Umbert Millet	2013/0131029 A1	5/2013	Carson et al.	
2011/0275584 A1	11/2011	Wilckens et al.	2013/0149314 A1	6/2013	King	
2011/0281832 A1	11/2011	Li et al.	2013/0164225 A1	6/2013	Zhou et al.	
2011/0287094 A1	11/2011	Penhasi et al.	2013/0164346 A1	6/2013	Bottoni et al.	
2011/0294738 A1	12/2011	Ren et al.	2013/0165744 A1	6/2013	Caron et al.	
2011/0300167 A1	12/2011	McMurtry et al.	2013/0178452 A1	7/2013	Queiroz	
2011/0301087 A1	12/2011	Mcbride et al.	2013/0183254 A1	7/2013	Tamarkin et al.	
2011/0306579 A1	12/2011	Stein	2013/0183253 A1	7/2013	Bottoni et al.	
2011/0318405 A1	12/2011	Erwin	2013/0189193 A1	7/2013	Tamarkin et al.	
2011/0318431 A1	12/2011	Gulati	2013/0189196 A1	7/2013	Tamarkin et al.	

US 9,114,146 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2013/0189230 A1	7/2013	Shoichet et al.	WO	WO2012166909 A1	12/2012	
2013/0189368 A1	7/2013	Mosqueira et al.	WO	WO2012170578 A1	12/2012	
2013/0210709 A1	8/2013	McMurtry et al.	WO	WO2012170578 A1	12/2012	
2013/0216550 A1	8/2013	Penninger et al.	WO	WO2013011501 A1	1/2013	
2013/0216596 A1	8/2013	Viladot Petit et al.	WO	WO2013025449 A1	2/2013	
2013/0224177 A1	8/2013	Kim et al.	WO	WO2013028639 A1	2/2013	
2013/0224257 A1	8/2013	Sah et al.	WO	WO2013035101 A1	3/2013	
2013/0224268 A1	8/2013	Alam et al.	WO	WO2013044067 A1	3/2013	
2013/0224300 A1	8/2013	Maggio	WO	WO2013045404 A2	4/2013	
2013/0225412 A1	8/2013	Sardari Lodriche et al.	WO	WO2013088254	6/2013	
2013/0225542 A1	8/2013	Poegh et al.	WO	WO2013102665 A1	7/2013	
2013/0226113 A1	8/2013	Schumacher et al.	WO	WO2013106437 A1	7/2013	
2013/0243696 A1	9/2013	Wang et al.	WO	WO2013113690	8/2013	
2013/0245253 A1	9/2013	Marx et al.	WO	WO2013124415 A1	8/2013	
2013/0245570 A1	9/2013	Jackson	WO	WO2013127727 A1	9/2013	
2013/0261096 A1	10/2013	Merian et al.	WO	WO2013127728 A1	9/2013	
2013/0266645 A1	10/2013	Becker et al.	WO	WO2013144356 A1	10/2013	
2013/0267485 A1	10/2013	Da Silva Maia Filho	WO	WO2013149258 A2	10/2013	
2013/0273167 A1	10/2013	Lee et al.	WO	WO2013158454 A2	10/2013	
2013/0274211 A1	10/2013	Burman et al.	WO	WO2013170052 A1	11/2013	
2013/0280213 A1	10/2013	Voskuhl	WO	2013192248	12/2013	
2013/0316374 A1	11/2013	Penninger et al.	WO	2013192249	12/2013	
2013/0317065 A1	11/2013	Tatani et al.	WO	2013192250	12/2013	
2013/0317315 A1	11/2013	Lu et al.	WO	2013192251	12/2013	
2013/0324565 A1	12/2013	Li et al.	WO	WO2013178587 A1	12/2013	
2013/0331363 A1	12/2013	Li et al.	WO	WO2013181449 A1	12/2013	
2013/0338124 A1	12/2013	Li et al.	WO	WO2014001904 A1	1/2014	
2013/0345187 A1	12/2013	Rodriguez Oquendo	WO	WO2014004424 A1	1/2014	
2014/0018335 A1	1/2014	Tatani et al.	WO	WO2014009434 A1	1/2014	
2014/0024590 A1	1/2014	Weidhaas et al.	WO	WO2014018569 A1	1/2014	
2014/0031289 A1	1/2014	Song et al.	WO	WO2014018570 A1	1/2014	
2014/0031323 A1	1/2014	Perez	WO	WO2014018571 A2	1/2014	
2014/0066416 A1	3/2014	Leunis et al.	WO	WO2014018856 A1	1/2014	
2014/0072531 A1	3/2014	Kim et al.	WO	WO2014018932 A1	1/2014	
2014/0079686 A1	3/2014	Barman et al.	WO	WO2014018932 A2	1/2014	
2014/0088058 A1	3/2014	Maurizio	WO	WO2014031958 A1	2/2014	
2014/0088059 A1	3/2014	Perumal et al.	WO	WO2014041120 A1	3/2014	
2014/0094426 A1	4/2014	Drummond et al.	WO	WO2014052792 A1	4/2014	
2014/0100159 A1	4/2014	Conrad	WO	WO2014056897 A1	4/2014	
2014/0100206 A1	4/2014	Bernick et al.	WO	WO2014066442 A2	5/2014	
2014/0113889 A1	4/2014	Connor et al.	WO	WO2014074846 A1	5/2014	
2014/0127185 A1	5/2014	Stein et al.	WO	WO2014076231 A1	5/2014	
2014/0127280 A1	5/2014	Duesterberg et al.	WO	WO2014076569 A2	5/2014	
2014/0127308 A1	5/2014	Opara et al.	WO	WO2014081598 A1	5/2014	
2014/0128798 A1	5/2014	Janson et al.	WO	WO2014086739 A1	6/2014	
2014/0148491 A1	5/2014	Valia et al.	WO	WO2014093114 A1	6/2014	
2014/0186332 A1	7/2014	Ezrin et al.	WO	WO2014104784 A1	7/2014	
2014/0187487 A1	7/2014	Shoichet et al.		OTHER PUBLICATIONS		
2014/0193523 A1	7/2014	Henry		Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.		
2014/0194396 A1	7/2014	Li et al.		Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.		
2014/0206616 A1	7/2014	Ko et al.		Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.		
2014/0371184 A1	12/2014	Bernick et al.		Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.		
2015/0031654 A1	1/2015	Amadio		Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.		
2015/0045335 A1	2/2015	Bernick et al.		Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.		
2015/0133421 A1	5/2015	Bernick et al.		Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.		
FOREIGN PATENT DOCUMENTS						
WO	WO03028667	4/2003		ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.		
WO	WO2004014432	2/2004		Abbas et al., Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis, European J of Pharma, 715 (2013) 72-75, Elsevier.		
WO	WO2005081825	9/2005				
WO	WO2007120868	10/2007				
WO	WO2010146872	12/2010				
WO	WO2012055814 A1	5/2012				
WO	WO2012055840 A1	5/2012				
WO	WO2012065740	5/2012				
WO	WO2012098090 A1	7/2012				
WO	WO2012116277 A1	8/2012				
WO	WO2012118563 A2	9/2012				
WO	WO2012120365 A1	9/2012				
WO	WO2012127501 A2	9/2012				
WO	WO2012156561 A1	11/2012				
WO	WO2012156822 A1	11/2012				
WO	WO2012158483 A2	11/2012				

US 9,114,146 B2

Page 6

(56)

References Cited

OTHER PUBLICATIONS

- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceuticals substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, *Menopause: The Journal of the North American Menopause Society*, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, *Advances in Therapy®*, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, *Yale J Biology and Medicine*, vol. 35, Feb. 1963, pp. 329-340.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, *Current Medicinal Chemistry*, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, *Biology of Reproduction* 52, 1327-1333 (1995).
- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductiveaged female subjects, *Fertility and Sterility*# vol. 94, No. 4, Sep. 2010, Elsevier.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, *J Clin Oncol* 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008; 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance , *Contact Dermatitis*, 71, 264-272, 2014.
- Cincinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, Mar. 2000, pp. 403-406.
- Critchley et al., Estrogen Receptor β , But Not Estrogen Receptor α , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene based on exposure and effect data, *Contact Dermatitis* 1990; 23: 341-345.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gäfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Gattefosé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Glaser et al, Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al, Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Herman, Anna et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, pp. 1-13.
- Hostynk, JJ, Predicting absorption of fragrances through human skin, *j. Soc.C osmeCt. hem.*, 4 6, 221-229 (Jul./Aug. 1995).
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, *Journal of Cerebral Blood Flow and Metabolism* 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 α -Ethynodiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 β -Estradiol, *JPET* 290(2):740-747, 1999.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, *J Reprod Fert* (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, *Environmental Health Perspectives* • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, *Contact Dermatitis*, 1992: 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, *Ann. Occup. Hyg.*, vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.

US 9,114,146 B2

Page 7

- (56) **References Cited**
- OTHER PUBLICATIONS**
- Komm et al., Bazedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Kumasaka et al., Effects of Various Forms of Progestin on the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2), 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol*. Jul. 2011 ; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVY IN OBGYN*, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol*. May 2010 ; 202(5): 455.e1-455.e9.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, *in vitro* and *ex vivo* characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration by Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Opinion on the Diethylene Glycol Momoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol*. Nov. 2008 ; 26(11): 1261-1268.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24,2007 The Dow Chemical Company Page, 5 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause A Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab*. 2014, 6: 139-143.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181,512-520 (2014).
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *Ann J Obstet Gynecol*, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010;5 943-954, Dove Press.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, *CLIMACTERIC* 2014;17:1-14.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, *Maturitas* 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, *Fertil Steril*. Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, *Toxicologic Pathology*, 42: 1188-1196, 2014.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, *Journal of Experimental & Clinical Cancer Research* 2014, 33(1):41, 11 pages.
- Stew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, *Pharmaceutical Technology*, Aug. 2014, pp. 28, 30-31.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," *Maturitas* 47 (2004) 277-283.
- Smyth et al., Summary of Toxicological Data, a 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats, *Fd Cosmet. Toxicol.* vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Therapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, *Contraception*, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause: The Journal of the North American Menopause Society*, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z., "All progestins are not created equal," *Steroids* 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" *Climacteric* 2014; 17(Suppl 2):8-11.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," *Int J Pharmaceutical Compounding*, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, *Alternative Medicine Review* vol. 12, No. 3, 2007, pp. 259-264.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, *Biology of Reproduction* 31, 399-413 (1984).
- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, *Gynecol Endocrinol*, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Thomas, Peter, Characteristics of membrane progestin receptor alpha (mPRA) and progesterone membrane receptor component 1

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Page 8

(56)

References Cited

OTHER PUBLICATIONS

- (PGMRC1) and their roles in mediating rapid progestin actions, *Frontiers in Neuroendocrinology* 29 (2008) 292-312.
- Ueda et al., Topical and Transdermal Drug Products, *Pharmacopeial Forum*, vol. 35(3) [May-Jun. 2009], 750-754.
- U.S. Appl. No. 13/843,362_Mar. 16, 2015_Restriction_Requirement.
- U.S. Appl. No. 13/843,428_Apr. 14, 2015_Restriction_Requirement.
- U.S. Appl. No. 14/099,545_Jul. 14, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,562_Mar. 27, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,562_Jul. 2, 2014_Final_Office_Action.
- U.S. Appl. No. 14/099,562_Dec. 10, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,571_Mar. 28, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,571_Jul. 15, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,582_Apr. 29, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,582_Jun. 17, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,582_Nov. 7, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,582_Jan. 22, 2015_Notice_of_Allowance.
- U.S. Appl. No. 14/099,598_May 13, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,598_Jul. 3, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,598_Dec. 10, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,612_Mar. 20, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,612_Oct. 30, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,612_Nov. 26, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,623_Jul. 18, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,623_Dec. 15, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/103,355_Dec. 8, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/106,655_Jul. 3, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/125,554_Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/125,554_Apr. 14, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/136,048_Nov. 4, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/136,048_Mar. 12, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,814_Oct. 1, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,814_Feb. 13, 2015_Notice_of_Allowance.
- U.S. Appl. No. 14/475,864_Feb. 11, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/475,864_Oct. 2, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/521,230_Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/521,230_Feb. 18, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/624,051_Apr. 7, 2015_Non-Final_Office_Action.
- Voegtlle et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.
- Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.
- Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role for the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).
- Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.
- Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforb.es/1LIUm1V> on Feb. 23, 2015, 3 pages.
- Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
- Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).
- Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.
- Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid.

* cited by examiner

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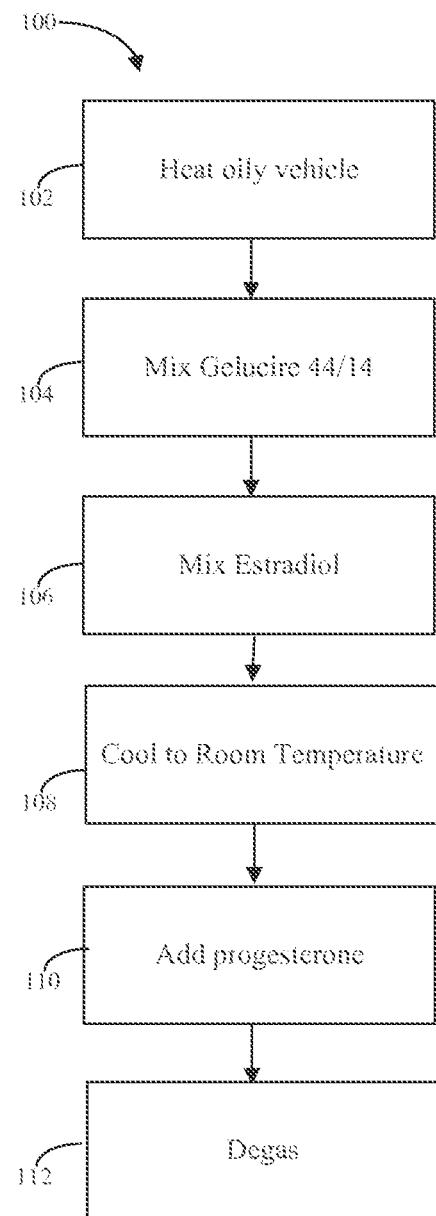
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Fig. 1

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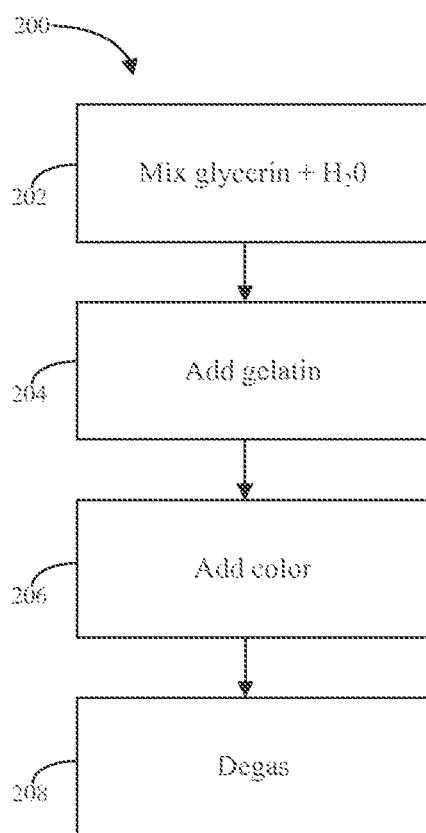


Fig. 2

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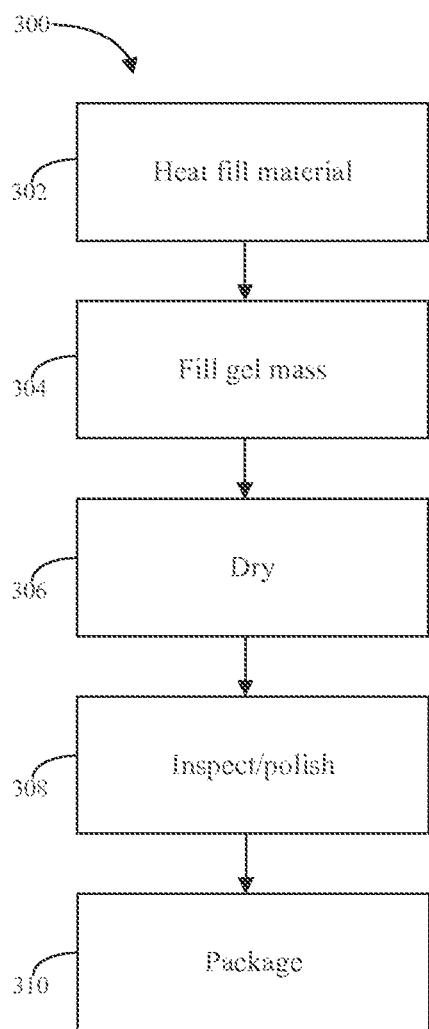


Fig. 3

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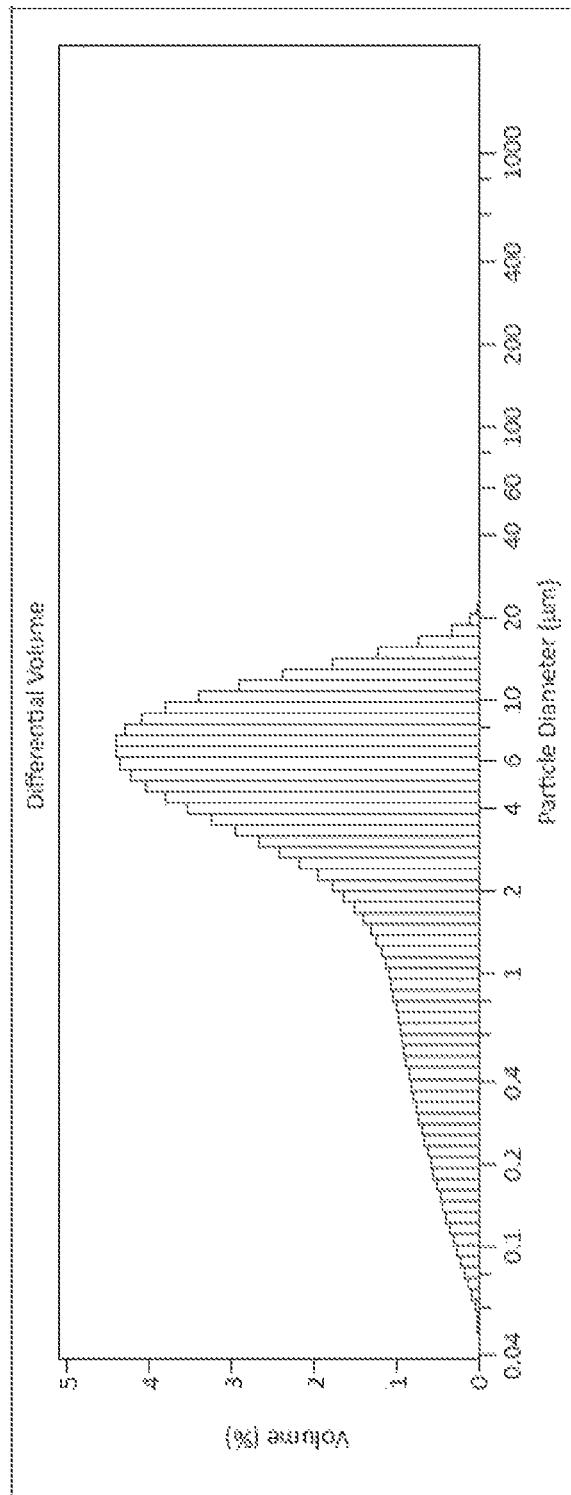


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCES TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which claims priority to the following U.S. Provisional patent applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

35 SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via 40 pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, 45 each in accordance with the invention are set forth below.

50 BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated 55 herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in 65 accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pk) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max}, and optionally, T_{max}.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, "C_{max}" as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, "T_{max}" as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating

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pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

5 The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

10 "Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

15 "Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. Description and Preferred Embodiments

20 Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, 25 aspects and embodiments are further defined herein.

30 Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

35 Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be 40 desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, 45 from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

50 Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra-

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and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

5 These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

10 Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

15 Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction 20 Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

25 The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm . The ULM is a liquid based 30 module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may 35 be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other 40 suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the 45 Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. 50 Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

55 The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may 60 use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These 65 formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other

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solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may

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contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and

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filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

	Ingredient	Solubility (mg/g)
10	PEG 400	105*
	Propylene Glycol	75*
15	Polysorbate 80	36*
	Transcutol HP	141
	Capmul PG8	31.2

*Literature reference—Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

	Ingredient	Solubility (mg/g)
45	Miglyol:Capmul PG8 (85:15)	4.40
	Miglyol:Capmul PG8 (70:30)	8.60
50	Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
	Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
	Miglyol:Capmul PG8 (50:50)	14.0
	Capmul MCM	19.8
55	Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Myglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF	82.57	577.97	
Gelucire 44/14, NF	10.0	70.00	
TOTAL	100.00	700.00	

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/-2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32- glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is

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removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

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TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
		Total:	100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
		Total:	100.000	200.00mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
		Total:	100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until

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dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study
Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condi-

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tion, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests 5 at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 10 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing 15 blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were 20 stored at a temperature of -70°C.±20°C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical composition comprising:
solubilized estradiol;
suspended progesterone;
and a solubilizing agent;
wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;
wherein at least about 90% of the estradiol is solubilized in
the solubilizing agent;

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and wherein the solubilizing agent comprises predominately a saturated C6-C12 oil.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. A pharmaceutical composition comprising:
solubilized estradiol;
suspended progesterone; and
a solubilizing agent, the solubilizing agent comprising predominately a saturated C6-C12 oil;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

7. The pharmaceutical composition of claim 6, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

8. The pharmaceutical composition of claim 6, wherein the composition is formulated as a gelatin capsule.

9. The pharmaceutical composition of claim 6, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

10. The pharmaceutical composition of claim 6, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

11. A method of treating menopause symptoms in a woman with a uterus comprising:

administering an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises predominately a saturated C6-C12 oil.

12. The method of claim 11, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

13. The method of claim 11, wherein the composition is formulated in a gelatin capsule.

14. The method of claim 11, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

15. The method of claim 11, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,114,146 B2
APPLICATION NO. : 14/476040
DATED : August 25, 2015
INVENTOR(S) : Brian A. Bernick et al.

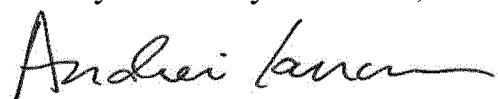
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT J



US009301920B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 9,301,920 B2
(45) **Date of Patent:** *Apr. 5, 2016

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 201 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Mar. 15, 2013**

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(60) Provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/662,265, filed on Jun. 20, 2012.

(51) **Int. Cl.**

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A61K 9/00	(2006.01)
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A61K 9/48	(2006.01)
A61K 47/10	(2006.01)
A61K 47/14	(2006.01)
A61K 9/107	(2006.01)
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(52) **U.S. Cl.**

CPC	A61K 9/0034 (2013.01); A61K 9/02 (2013.01); A61K 9/1075 (2013.01); A61K 9/48 (2013.01); A61K 9/4858 (2013.01); A61K 9/4866 (2013.01); A61K 31/565 (2013.01); A61K 31/57 (2013.01); A61K 47/10 (2013.01); A61K 47/14 (2013.01); A61K 47/44 (2013.01)
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(58) **Field of Classification Search**

USPC 514/170, 899

See application file for complete search history.

(56)

References Cited

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934 Dolay
2,232,438 A	2/1941 Butenandt
2,379,832 A	7/1945 Serini et al.
2,649,399 A	8/1953 Beall et al.
3,198,707 A	8/1965 Nomine et al.
3,478,070 A	11/1969 Stein et al.
3,526,648 A	9/1970 Bertin et al.
3,710,795 A	1/1973 Higuchi et al.
3,729,560 A	4/1973 Hagerman
3,729,566 A	4/1973 Ericsson et al.
3,755,573 A	8/1973 Berman
3,755,575 A	8/1973 Lerner
3,903,880 A	9/1975 Higuchi et al.
3,916,898 A	11/1975 Robinson
3,916,899 A	11/1975 Theeuwes et al.
3,921,636 A	11/1975 Zaffaroni
3,923,997 A	12/1975 Meuly
3,948,254 A	4/1976 Zaffaroni
3,971,367 A	7/1976 Zaffaroni
3,977,404 A	8/1976 Theeuwes
3,993,072 A	11/1976 Zaffaroni
4,008,719 A	2/1977 Theeuwes et al.
4,012,496 A	3/1977 Schopflin et al.
4,014,334 A	3/1977 Theeuwes et al.
4,014,987 A	3/1977 Heller et al.
4,016,251 A	4/1977 Higuchi et al.
4,071,623 A	1/1978 van der Vies
4,093,709 A	6/1978 Choi et al.
4,154,820 A	5/1979 Simoons
4,155,991 A	5/1979 Schopflin et al.
4,196,188 A	4/1980 Besins
4,215,691 A	8/1980 Wong
4,237,885 A	12/1980 Wong et al.

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI 1001367-9 A2	7/2012
CN	102258455 A	11/2011

(Continued)

OTHER PUBLICATIONS

International Search Report and Written Opinion for PCT/US13/46442, dated Nov. 1, 2013.

International Search Report and Written Opinion for PCT/US13/46443, dated Oct. 31, 2013.

International Search Report and Written Opinion for PCT/US13/46444, dated Oct. 31, 2013.

International Search Report and Written Opinion for PCT/US13/46445, dated Nov. 1, 2013.

(Continued)

Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

14 Claims, 5 Drawing Sheets

US 9,301,920 B2

Page 2

(56)

References Cited**U.S. PATENT DOCUMENTS**

4,310,510 A	1/1982	Sherman et al.	5,677,292 A	10/1997	Li et al.
4,327,725 A	5/1982	Cortese et al.	5,686,097 A	11/1997	Taskovich et al.
4,372,951 A	2/1983	Vorys	5,693,335 A	12/1997	Xia et al.
4,384,096 A	5/1983	Sonnabend	5,694,947 A	12/1997	Lehtinen et al.
4,393,871 A	7/1983	Vorhauer et al.	5,700,480 A	12/1997	Hille et al.
4,402,695 A	9/1983	Wong	5,709,844 A	1/1998	Arbeit et al.
4,423,151 A	12/1983	Baranczuk	5,719,197 A	2/1998	Kanios et al.
4,449,980 A	5/1984	Millar et al.	5,735,801 A	4/1998	Caillouette
4,610,687 A	9/1986	Fogwell	5,739,176 A	4/1998	Dunn et al.
4,629,449 A	12/1986	Wong	5,744,463 A	4/1998	Bair
4,732,763 A	3/1988	Beck et al.	5,747,058 A	5/1998	Tipton et al.
4,738,957 A	4/1988	Laurent et al.	5,770,219 A	6/1998	Chiang et al.
4,756,907 A	7/1988	Beck et al.	5,770,220 A	6/1998	Meconi et al.
4,762,717 A	8/1988	Crowley, Jr.	5,770,227 A	6/1998	Dong et al.
4,788,062 A	11/1988	Gale et al.	5,776,495 A	7/1998	Duclos et al.
4,816,257 A	3/1989	Buster et al.	5,780,044 A	7/1998	Yewey et al.
4,822,616 A	4/1989	Zimmermann et al.	5,780,050 A	7/1998	Jain et al.
4,865,848 A	9/1989	Cheng et al.	5,788,980 A	8/1998	Nabahi
4,900,734 A	2/1990	Maxson et al.	5,788,984 A	8/1998	Guenther et al.
4,906,475 A	3/1990	Kim	5,789,442 A	8/1998	Garfield et al.
4,942,158 A	7/1990	Sarpotdar et al.	5,811,416 A	9/1998	Chwalisz et al.
4,961,931 A	10/1990	Wong	5,811,547 A	9/1998	Nakamichi et al.
5,030,629 A	7/1991	Rajadhyaksha	5,814,329 A	9/1998	Shah
5,064,654 A	11/1991	Berner et al.	5,820,878 A	10/1998	Hirano et al.
5,108,995 A	4/1992	Casper	5,827,200 A	10/1998	Caillouette
5,128,138 A	7/1992	Blank	5,840,327 A	11/1998	Gale et al.
5,130,137 A	7/1992	Crowley, Jr.	5,843,468 A	12/1998	Burkoth et al.
5,140,021 A	8/1992	Maxson et al.	5,843,979 A	12/1998	Wille et al.
5,211,952 A	5/1993	Spicer et al.	5,858,394 A	1/1999	Lipp et al.
5,252,334 A	10/1993	Chiang et al.	5,863,552 A	1/1999	Yue
5,280,023 A	1/1994	Ehrlich et al.	5,866,603 A	2/1999	Li et al.
5,288,496 A	2/1994	Lewis	5,882,676 A	3/1999	Lee et al.
5,340,584 A	8/1994	Spicer et al.	5,885,612 A	3/1999	Meconi et al.
5,340,585 A	8/1994	Pike et al.	5,888,533 A	3/1999	Dunn
5,340,586 A	8/1994	Pike et al.	5,891,462 A	4/1999	Carrara
5,362,497 A	11/1994	Yamada et al.	5,891,868 A	4/1999	Cummings et al.
5,382,573 A	1/1995	Casper	5,898,038 A	4/1999	Yallampalli et al.
5,393,528 A	2/1995	Staab	5,902,603 A	5/1999	Chen et al.
5,393,529 A	2/1995	Hoffmann et al.	5,904,931 A	5/1999	Lipp et al.
5,419,910 A	5/1995	Lewis	5,906,830 A	5/1999	Farinas et al.
5,468,736 A	11/1995	Hodgen	5,912,010 A	6/1999	Wille et al.
5,474,783 A	12/1995	Miranda et al.	5,916,176 A	6/1999	Caillouette
5,480,776 A	1/1996	Dullien	RE36,247 E	7/1999	Plunkett et al.
5,514,673 A	5/1996	Heckenmueller et al.	5,919,477 A	7/1999	Bevan et al.
5,516,528 A	5/1996	Hughes et al.	5,922,349 A	7/1999	Elliesen et al.
5,527,534 A	6/1996	Myhling	5,928,666 A	7/1999	Farinas et al.
5,529,782 A	6/1996	Staab	5,942,243 A	8/1999	Shah
5,538,736 A	7/1996	Hoffmann et al.	5,942,531 A	8/1999	Diaz et al.
5,543,150 A	8/1996	Bologna et al.	5,952,000 A	9/1999	Venkateshwaran et al.
5,547,948 A	8/1996	Barcomb	5,958,446 A	9/1999	Miranda et al.
5,556,635 A	9/1996	Istin et al.	5,962,445 A	10/1999	Stewart
5,565,199 A	10/1996	Page et al.	5,968,919 A	10/1999	Samour et al.
5,567,831 A	10/1996	Li	5,972,372 A	10/1999	Saleh et al.
5,569,652 A	10/1996	Beier et al.	5,985,311 A	11/1999	Cordes et al.
5,580,572 A	12/1996	Mikler et al.	5,985,850 A	11/1999	Falk et al.
5,582,592 A	12/1996	Kendrick	5,985,861 A	11/1999	Levine et al.
5,585,370 A	12/1996	Casper	5,989,568 A	11/1999	Bretton et al.
5,595,759 A	1/1997	Wright et al.	5,993,856 A	11/1999	Ragavan et al.
5,595,970 A	1/1997	Garfield et al.	6,001,846 A	12/1999	Edwards et al.
5,605,702 A	2/1997	Teillaud et al.	6,007,835 A	12/1999	Bon-Lapillon et al.
5,607,691 A	3/1997	Hale et al.	6,010,715 A	1/2000	Wick et al.
5,607,693 A	3/1997	Bonte et al.	6,013,276 A	1/2000	Math et al.
5,609,617 A	3/1997	Shealy et al.	6,022,562 A	2/2000	Autant et al.
5,620,705 A	4/1997	Dong et al.	6,024,974 A	2/2000	Li
5,626,866 A	5/1997	Ebert et al.	6,024,976 A	2/2000	Miranda et al.
5,629,021 A	5/1997	Wright	6,028,057 A	2/2000	Burns
5,633,011 A	5/1997	Dong et al.	6,030,948 A	2/2000	Mann
5,633,242 A	5/1997	Oettel et al.	6,039,968 A	3/2000	Nabahi
5,639,743 A	6/1997	Kaswan et al.	6,040,340 A	3/2000	Chwalisz et al.
5,653,983 A	8/1997	Meybeck et al.	6,056,972 A	5/2000	Hermsmeyer
5,656,286 A	8/1997	Miranda et al.	6,060,077 A	5/2000	Meignant
5,660,839 A	8/1997	Allec et al.	6,068,853 A	5/2000	Giannos et al.
5,662,927 A	9/1997	Ehrlich et al.	6,074,625 A	6/2000	Hawthorne et al.
5,663,160 A	9/1997	Meybeck et al.	6,077,531 A	6/2000	Salin-Drouin
5,676,968 A	10/1997	Lipp et al.	6,080,118 A	6/2000	Blythe
			6,083,178 A	7/2000	Caillouette
			6,086,916 A	7/2000	Agnus et al.
			6,087,352 A	7/2000	Trot
			6,090,404 A	7/2000	Meconi et al.

US 9,301,920 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

6,096,338 A	8/2000	Lacy et al.	6,521,250 B2	2/2003	Meconi et al.
6,106,848 A	8/2000	Preuilh et al.	6,526,980 B1	3/2003	Tracy et al.
6,117,446 A	9/2000	Place	6,528,094 B1	3/2003	Savoir et al.
6,117,450 A	9/2000	Dittgen et al.	6,531,149 B1	3/2003	Kirstgen et al.
6,124,362 A	9/2000	Bradbury et al.	6,537,580 B1	3/2003	Savoir et al.
6,133,251 A	10/2000	Dittgen et al.	6,538,039 B2	3/2003	Laurent
6,133,320 A	10/2000	Yallampalli et al.	6,544,196 B2	4/2003	Caillouette
6,139,868 A	10/2000	Hoffmann	6,544,553 B1	4/2003	Hsia et al.
6,139,873 A	10/2000	Hughes, Jr. et al.	6,548,053 B1	4/2003	Stewart et al.
6,149,935 A	11/2000	Chiang et al.	6,548,491 B2	4/2003	Tanabe et al.
6,153,216 A	11/2000	Cordes et al.	6,551,611 B2	4/2003	Elliesen et al.
6,165,491 A	12/2000	Grasset et al.	6,555,131 B1	4/2003	Wolff et al.
6,165,975 A	12/2000	Adams et al.	6,562,367 B1	5/2003	Wolff et al.
6,187,323 B1	2/2001	Aiache et al.	6,562,370 B2	5/2003	Luo et al.
6,187,339 B1	2/2001	de Haan et al.	6,562,790 B2	5/2003	Chein
6,190,331 B1	2/2001	Caillouette	6,569,463 B2	5/2003	Patel et al.
6,201,072 B1	3/2001	Rathi et al.	6,583,129 B1	6/2003	Mazer et al.
6,217,886 B1	4/2001	Onyueksel et al.	6,610,670 B2	8/2003	Backensfeld et al.
6,225,297 B1	5/2001	Stockemann et al.	6,610,674 B1	8/2003	Schreiber
6,227,202 B1	5/2001	Matapurkar	6,635,274 B1	10/2003	Masiz et al.
6,228,383 B1	5/2001	Hansen et al.	6,638,528 B1	10/2003	Kanios
6,228,852 B1	5/2001	Shaak	6,638,536 B2	10/2003	Savoir et al.
6,242,509 B1	6/2001	Berger et al.	6,645,528 B1	11/2003	Straub et al.
6,245,811 B1	6/2001	Horrobin et al.	6,649,155 B1	11/2003	Dunlop et al.
6,262,115 B1	7/2001	Guittard et al.	6,653,298 B2	11/2003	Potter et al.
6,267,984 B1	7/2001	Beste et al.	6,656,929 B1	12/2003	Agnus et al.
6,274,165 B1	8/2001	Meconi et al.	6,660,726 B2	12/2003	Hill et al.
6,277,418 B1	8/2001	Markaverich et al.	6,663,608 B2	12/2003	Rathbone et al.
6,283,927 B1	9/2001	Caillouette	6,663,895 B2	12/2003	Savoir et al.
6,287,588 B1	9/2001	Shih et al.	6,682,757 B1	1/2004	Wright
6,287,693 B1	9/2001	Savoir et al.	6,692,763 B1	2/2004	Cummings et al.
6,294,188 B1	9/2001	Ragavan et al.	6,708,822 B1	3/2004	Muni
6,294,192 B1	9/2001	Patel et al.	6,720,001 B2	4/2004	Chen et al.
6,294,550 B1	9/2001	Place et al.	6,737,081 B2	5/2004	Savoir et al.
6,299,900 B1	10/2001	Reed et al.	6,740,333 B2	5/2004	Beckett et al.
6,303,132 B1	10/2001	Nelson	6,743,448 B2	6/2004	Kryger
6,303,588 B1	10/2001	Danielov	6,743,815 B2	6/2004	Huebner et al.
6,306,841 B1	10/2001	Place et al.	6,747,018 B2	6/2004	Tanabe et al.
6,306,914 B1	10/2001	de Ziegler et al.	6,750,291 B2	6/2004	Kim et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,756,208 B2	6/2004	Griffin et al.
6,309,848 B1	10/2001	Howett et al.	6,776,164 B2	8/2004	Bunt et al.
6,312,703 B1	11/2001	Orthofer	6,787,152 B2	9/2004	Kirby et al.
6,328,987 B1	12/2001	Marini	6,805,877 B2	10/2004	Massara et al.
6,342,491 B1	1/2002	Dey et al.	6,809,085 B1	10/2004	Elson et al.
6,344,211 B1	2/2002	Hille	6,818,226 B2	11/2004	Reed et al.
6,372,209 B1	4/2002	Chrisope	6,821,524 B2	11/2004	Marini
6,372,245 B1	4/2002	Bowman et al.	6,841,716 B1	1/2005	Tsutsumi
6,372,246 B1	4/2002	Wei et al.	6,844,334 B2	1/2005	Hill et al.
6,387,390 B1	5/2002	Deaver et al.	6,855,703 B1	2/2005	Hill et al.
6,402,705 B1	6/2002	Caillouette	6,860,859 B2	3/2005	Mehrotra et al.
6,416,778 B1	7/2002	Ragavan et al.	6,866,865 B2	3/2005	Hsia et al.
6,420,352 B1	7/2002	Knowles	6,869,969 B2	3/2005	Huebner et al.
6,423,039 B1	7/2002	Rathbone et al.	6,878,518 B2	4/2005	Whitehead
6,423,683 B1	7/2002	Heaton et al.	6,901,278 B1	5/2005	Notelovitz
6,432,438 B1	8/2002	Shukla	6,905,705 B2	6/2005	Palm et al.
6,436,633 B1	8/2002	Kreider et al.	6,911,211 B2	6/2005	Eini et al.
6,440,454 B1	8/2002	Santoro et al.	6,911,438 B2	6/2005	Wright
6,444,224 B1	9/2002	Rathbone et al.	6,923,988 B2	8/2005	Patel et al.
6,444,234 B1	9/2002	Kirby et al.	6,924,274 B2	8/2005	Lardy et al.
6,451,300 B1	9/2002	Dunlop et al.	6,932,983 B1	8/2005	Straub et al.
6,451,339 B2	9/2002	Patel et al.	6,939,558 B2	9/2005	Massara et al.
6,451,779 B1	9/2002	Hesch	6,943,021 B2	9/2005	Klausner et al.
6,455,246 B1	9/2002	Howett et al.	6,958,327 B1	10/2005	Hillisch et al.
6,455,517 B1	9/2002	Tanabe et al.	6,960,337 B2	11/2005	Daniels et al.
6,465,004 B1	10/2002	Rossi Montero et al.	6,962,691 B1	11/2005	Lulla et al.
6,465,005 B1	10/2002	Biali et al.	6,962,908 B2	11/2005	Aloba et al.
6,465,006 B1	10/2002	Zhang et al.	6,967,194 B1	11/2005	Matsu et al.
6,468,526 B2	10/2002	Chrisope	6,974,569 B2	12/2005	Dunlop et al.
6,469,016 B1	10/2002	Place et al.	6,977,250 B2	12/2005	Rodriguez
6,472,434 B1	10/2002	Place et al.	6,978,945 B2	12/2005	Wong et al.
6,479,232 B1	11/2002	Howett et al.	6,995,149 B1	2/2006	Endrikat et al.
6,495,160 B2	12/2002	Esposito et al.	7,004,321 B1	2/2006	Palm et al.
6,500,814 B1	12/2002	Hesch	7,005,429 B2	2/2006	Dey et al.
6,503,896 B1	1/2003	Tanabe et al.	7,011,846 B2	3/2006	Shojaei et al.

US 9,301,920 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
7,018,992 B2	3/2006	Koch et al.	7,867,990 B2	1/2011	Schultz et al.	
7,030,104 B2	4/2006	Gray et al.	7,871,643 B2	1/2011	Lizio et al.	
7,030,157 B2	4/2006	Ke et al.	7,879,830 B2	2/2011	Wiley	
RE39,104 E	5/2006	Duclos et al.	7,884,093 B2	2/2011	Creasy et al.	
7,074,779 B2	7/2006	Sui et al.	7,925,519 B2	4/2011	Greene	
7,083,590 B1	8/2006	Bunt et al.	7,939,104 B2	5/2011	Barbera et al.	
7,091,213 B2	8/2006	Metcalf, III et al.	7,943,602 B2	5/2011	Bunschoten et al.	
7,094,228 B2	8/2006	Zhang et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.	
7,097,853 B1	8/2006	Garbe et al.	7,945,459 B2	5/2011	Grace et al.	
7,101,342 B1	9/2006	Caillouette	7,960,368 B2	6/2011	Nickisch et al.	
7,105,573 B2	9/2006	Krajcik et al.	7,989,436 B2	8/2011	Hill et al.	
7,135,190 B2	11/2006	Piao et al.	7,989,487 B2	8/2011	Welsh et al.	
7,153,522 B1	12/2006	Ikeura et al.	8,022,053 B2	9/2011	Mueller et al.	
7,163,681 B2	1/2007	Giles-Komar et al.	8,048,017 B2	11/2011	Xu	
7,163,699 B2	1/2007	Besse	8,048,869 B2	11/2011	Bunschoten et al.	
7,175,850 B2	2/2007	Cevc	8,063,030 B2	11/2011	Ellman	
7,179,799 B2	2/2007	Hill et al.	8,071,576 B2	12/2011	Coelingh Bennink et al.	
7,196,074 B2	3/2007	Blye et al.	8,071,729 B2	12/2011	Giles-Komar et al.	
7,198,800 B1	4/2007	Ko	8,075,916 B2	12/2011	Song et al.	
7,198,801 B2	4/2007	Carrara et al.	8,075,917 B2	12/2011	Chung et al.	
7,226,910 B2	6/2007	Wilson et al.	8,096,940 B2	1/2012	Josephson et al.	
7,247,625 B2	7/2007	Zhang et al.	8,101,209 B2	1/2012	Legrand et al.	
7,250,446 B2	7/2007	Sangita et al.	8,114,152 B2	2/2012	Furst	
7,267,829 B2	9/2007	Kirby et al.	8,114,434 B2	2/2012	Sasaki et al.	
7,300,926 B2	11/2007	Prokai et al.	8,114,442 B2	2/2012	Tucker et al.	
7,303,763 B2	12/2007	Ho	8,119,741 B2	2/2012	Pavlin	
7,317,037 B2	1/2008	Fensome et al.	8,121,886 B2	2/2012	Azar	
7,329,654 B2	2/2008	Kanojia et al.	8,124,118 B2	2/2012	Lennernaes et al.	
7,335,650 B2	2/2008	Potter et al.	8,124,595 B2	2/2012	Boissonneault	
7,374,779 B2	5/2008	Chen et al.	8,147,561 B2	4/2012	Binmoeller	
7,378,404 B2	5/2008	Peters et al.	8,148,546 B2	4/2012	Schuster et al.	
7,381,427 B2	6/2008	Ancira et al.	8,158,613 B2	4/2012	Staniforth et al.	
7,387,789 B2	6/2008	Klose et al.	8,158,614 B2	4/2012	Lambert et al.	
7,388,006 B2	6/2008	Schmees et al.	8,163,722 B2	4/2012	Savoir et al.	
7,414,043 B2	8/2008	Kosemund et al.	8,177,449 B2	5/2012	Bayly et al.	
7,427,413 B2	9/2008	Savoir et al.	8,182,833 B2	5/2012	Hermsmeyer	
7,427,609 B2	9/2008	Leonard	8,187,615 B2	5/2012	Friedman	
7,429,576 B2	9/2008	Labrie	8,187,640 B2	5/2012	Dunn	
7,431,941 B2	10/2008	Besins et al.	8,195,403 B2	6/2012	Ishikawa et al.	
7,456,159 B2	11/2008	Houze et al.	8,202,736 B2	6/2012	Mousa et al.	
7,459,445 B2	12/2008	Hill et al.	8,217,024 B2	7/2012	Ahmed et al.	
7,465,587 B2	12/2008	Imrich	8,221,785 B2	7/2012	Chien	
7,470,433 B2	12/2008	Carrara et al.	8,222,008 B2	7/2012	Thoene	
7,485,666 B2	2/2009	Villanueva et al.	8,222,237 B2	7/2012	Nickisch et al.	
7,497,855 B2	3/2009	Ausiello et al.	8,227,454 B2	7/2012	Hill et al.	
7,498,303 B2	3/2009	Arnold et al.	8,227,509 B2	7/2012	Castro et al.	
7,534,765 B2	5/2009	Gregg et al.	8,241,664 B2	8/2012	Dudley et al.	
7,534,780 B2	5/2009	Wyrwa et al.	8,247,393 B2	8/2012	Ahmed et al.	
7,550,142 B2	6/2009	Giles-Komar et al.	8,257,724 B2	9/2012	Cromack et al.	
7,563,565 B1	7/2009	Matsuo et al.	8,257,725 B2	9/2012	Cromack et al.	
7,569,274 B2	8/2009	Besse et al.	8,268,352 B2	9/2012	Vaya et al.	
7,572,779 B2	8/2009	Aloba et al.	8,268,806 B2	9/2012	Labrie	
7,572,780 B2	8/2009	Hermsmeyer	8,268,878 B2	9/2012	Armer et al.	
7,589,082 B2	9/2009	Savoir et al.	8,273,730 B2	9/2012	Fernandez et al.	
7,671,027 B2	3/2010	Loumaye	8,287,888 B2	10/2012	Song et al.	
7,674,783 B2	3/2010	Hermsmeyer	8,288,366 B2	10/2012	Chochinov et al.	
7,687,281 B2	3/2010	Roth et al.	8,318,898 B2	11/2012	Fasel et al.	
7,687,485 B2	3/2010	Levinson et al.	8,324,193 B2	12/2012	Lee Sepsick et al.	
7,694,683 B2	4/2010	Callister et al.	8,329,680 B2	12/2012	Evans et al.	
7,704,983 B1	4/2010	Hodgen et al.	8,337,814 B2	12/2012	Osbakken et al.	
7,727,720 B2	6/2010	Dhallan	8,344,007 B2	1/2013	Tang et al.	
7,732,408 B2	6/2010	Josephson et al.	8,349,820 B2	1/2013	Zeun et al.	
7,749,989 B2	7/2010	Hill et al.	8,353,863 B2	1/2013	Imran	
7,767,656 B2	8/2010	Shoichet et al.	8,357,723 B2	1/2013	Satyam	
7,799,769 B2	9/2010	White et al.	8,361,995 B2	1/2013	Schramm	
7,815,936 B2	10/2010	Hasenzahl et al.	8,362,091 B2	1/2013	Tamarkin et al.	
7,815,949 B2	10/2010	Cohen	8,372,424 B2	2/2013	Berry et al.	
7,829,115 B2	11/2010	Besins et al.	8,372,806 B2	2/2013	Boehler et al.	
7,829,116 B2	11/2010	Griswold et al.	8,377,482 B2	2/2013	Laurie et al.	
RE42,012 E	12/2010	Deaver et al.	8,377,994 B2	2/2013	Gray et al.	
7,850,992 B2	12/2010	Kim et al.	8,394,759 B2	3/2013	Barathur et al.	
7,854,753 B2	12/2010	Kraft et al.	8,415,332 B2	4/2013	Diliberti et al.	
7,858,607 B2	12/2010	Mamchur	8,420,111 B2	4/2013	Hermsmeyer	
RE42,072 E	1/2011	Deaver et al.	8,435,561 B2	5/2013	Besins et al.	
7,862,552 B2	1/2011	McIntyre et al.	8,435,972 B2	5/2013	Stein et al.	

US 9,301,920 B2

Page 5

(56)

References Cited**U.S. PATENT DOCUMENTS**

8,449,879 B2	5/2013	Laurent Applegate et al.	2002/0058926 A1	5/2002	Rathbone et al.
8,450,108 B2	5/2013	Boyce	2002/0064541 A1	5/2002	Lapidot et al.
8,454,945 B2	6/2013	Mccook et al.	2002/0076441 A1	6/2002	Shih et al.
8,455,468 B2	6/2013	Hoffman et al.	2002/0119198 A1	8/2002	Wei et al.
8,461,138 B2	6/2013	Boissonneault	2002/0132801 A1	8/2002	Waldon et al.
8,476,252 B2	7/2013	Achleitner et al.	2002/0137749 A1	9/2002	Deaver et al.
8,481,488 B2	7/2013	Carter	2002/0142017 A1	8/2002	Gardlik et al.
8,486,374 B2	7/2013	Tamarkin et al.	2002/0151530 A1	10/2002	Gao et al.
8,486,442 B2	7/2013	Matsushita et al.	2002/0156394 A1	10/2002	Levinson et al.
8,492,368 B2	7/2013	Vanlandingham et al.	2002/0169150 A1	11/2002	Mehrotra et al.
8,507,467 B2	8/2013	Matsui et al.	2002/0169205 A1	11/2002	Simonnet
8,512,693 B2	8/2013	Capito et al.	2002/0173510 A1	11/2002	Van Beek et al.
8,512,754 B2	8/2013	Needham	2002/0193356 A1	12/2002	Bunt et al.
8,518,376 B2	8/2013	Tamarkin et al.	2002/0193758 A1	12/2002	Sandberg
8,536,159 B2	9/2013	Li et al.	2002/0197286 A1	12/2002	Gyurik
8,540,967 B2	9/2013	Barrett et al.	2003/0003139 A1	1/2003	Brandman et al.
8,541,400 B2	9/2013	Johnsson et al.	2003/0004145 A1	1/2003	Lipp et al.
8,551,462 B2	10/2013	Goldstein et al.	2003/0007994 A1	1/2003	Leonard
8,557,281 B2	10/2013	Halliday et al.	2003/0027772 A1	1/2003	Bunt et al.
8,568,374 B2	10/2013	De Graaff et al.	2003/0044453 A1	1/2003	Bretton
8,591,951 B2	11/2013	Kohn et al.	2003/0049307 A1	1/2003	Dittgen et al.
8,613,951 B2	12/2013	Zale et al.	2003/0064097 A1	1/2003	Chwalisz et al.
8,633,178 B2	1/2014	Bernick et al.	2003/0072760 A1	1/2003	Patel et al.
8,633,180 B2	1/2014	Li et al.	2003/0073248 A1	1/2003	Sirbasku
8,636,787 B2	1/2014	Sabaria	2003/0073673 A1	1/2003	Roth et al.
8,636,982 B2	1/2014	Tamarkin et al.	2003/0077297 A1	1/2003	Hesch
8,653,129 B2	2/2014	Fein et al.	2003/0078245 A1	1/2003	Chen et al.
8,658,627 B2	2/2014	Voskuhl	2003/0091620 A1	1/2003	Bennink et al.
8,658,628 B2	2/2014	Baucom	2003/0091640 A1	1/2003	Fikstad et al.
8,663,681 B2	3/2014	Ahmed et al.	2003/0092691 A1	1/2003	Ramanathan et al.
8,663,692 B1	3/2014	Mueller et al.	2003/0096012 A1	1/2003	Besse et al.
8,663,703 B2	3/2014	Lerner et al.	2003/0104048 A1	1/2003	Besse et al.
8,664,207 B2	3/2014	Li et al.	2003/0109507 A1	1/2003	Franke et al.
8,669,293 B2	3/2014	Levy et al.	2003/0113268 A1	1/2003	Buenafae et al.
8,679,552 B2	3/2014	Guthery	2003/0114420 A1	1/2003	Salvati et al.
8,694,358 B2	4/2014	Tryfon	2003/0114430 A1	1/2003	Shojaei et al.
8,697,127 B2	4/2014	Sah	2003/0124182 A1	1/2003	Besse et al.
8,697,710 B2	4/2014	Li et al.	2003/0124191 A1	1/2003	Massara et al.
8,703,105 B2	4/2014	Tamarkin et al.	2003/0130558 A1	1/2003	Heil et al.
8,709,385 B2	4/2014	Tamarkin et al.	2003/0144258 A1	1/2003	MacLeod et al.
8,709,451 B2	4/2014	Nam et al.	2003/0157157 A1	1/2003	Edwards et al.
8,715,735 B2	5/2014	Funke et al.	2003/0166509 A1	1/2003	Kim et al.
8,721,331 B2	5/2014	Raghuprasad	2003/0170295 A1	1/2003	Azarnoff et al.
8,722,021 B2	5/2014	Friedman et al.	2003/0175329 A1	1/2003	Shefer et al.
8,734,846 B2	5/2014	Ali et al.	2003/0175333 A1	1/2003	Patel et al.
8,735,381 B2	5/2014	Podolski	2003/0180352 A1	1/2003	Nyce
8,741,336 B2	6/2014	Dipierro et al.	2003/0181353 A1	1/2003	Salvati et al.
8,741,373 B2	6/2014	Bromley et al.	2003/0181728 A1	1/2003	Leonard et al.
8,753,661 B2	6/2014	Steinmueller Nethl et al.	2003/0191096 A1	1/2003	Grawe et al.
8,784,882 B2	7/2014	Mattern	2003/0195177 A1	1/2003	Klausner et al.
8,846,648 B2	9/2014	Bernick et al.	2003/0215496 A1	1/2003	Cauble et al.
8,846,649 B2	9/2014	Bernick et al.	2003/0219402 A1	1/2003	Rutter
8,933,059 B2	1/2015	Bernick et al.	2003/0220297 A1	1/2003	Berstein et al.
8,987,237 B2	3/2015	Bernick et al.	2003/0224057 A1	1/2003	Martin-Letellier et al.
8,987,238 B2	3/2015	Bernick et al.	2003/0224059 A1	1/2003	Lerner et al.
8,993,548 B2	3/2015	Bernick et al.	2003/0225047 A1	1/2003	Cauble et al.
8,993,549 B2	3/2015	Bernick et al.	2003/0225048 A1	1/2003	Cauble et al.
9,006,222 B2	4/2015	Bernick et al.	2003/0225050 A1	1/2003	Chen et al.
9,012,434 B2	4/2015	Bernick et al.	2003/0228686 A1	1/2003	Gao et al.
2001/0005728 A1	6/2001	Guittard et al.	2003/0229057 A1	1/2003	Heil et al.
2001/0009673 A1	7/2001	Lipp et al.	2003/0235596 A1	1/2003	Anderson
2001/0021816 A1	9/2001	Caillouette	2003/0236236 A1	1/2003	Karara
2001/0023261 A1	9/2001	Ryoo et al.	2004/0009960 A1	1/2004	Grawe et al.
2001/0027189 A1	10/2001	Bennink et al.	2004/0022820 A1	2/2004	Guittard et al.
2001/0029357 A1	10/2001	Bunt et al.	2004/0034001 A1	2/2004	Maki et al.
2001/0031747 A1	10/2001	deZiegler et al.	2004/0037881 A1	2/2004	Schlyter et al.
2001/0032125 A1	10/2001	Bhan et al.	2004/0039356 A1	2/2004	Place et al.
2001/0034340 A1	10/2001	Pickar	2004/0043043 A1	3/2004	Flood
2001/0053383 A1	12/2001	Miranda et al.	2004/0043943 A1	3/2004	Abou Chakra-Vernet et al.
2001/0056068 A1	12/2001	Chwalisz et al.	2004/0044080 A1	3/2004	Metcalf, III et al.
2002/0012710 A1	1/2002	Lansky	2004/0048900 A1	4/2004	Salvati et al.
2002/0026158 A1	2/2002	Rathbone et al.	2004/0052824 A1	4/2004	Salvati et al.
2002/0028788 A1	3/2002	Bunt et al.	2004/0073024 A1	4/2004	Guittard et al.
2002/0035070 A1	3/2002	Gardlik et al.	2004/0077605 A1	4/2004	Guittard et al.
2002/0058648 A1	5/2002	Hammerly	2004/0077606 A1	4/2004	Metcalfe et al.

US 9,301,920 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2004/0087548 A1	5/2004	Salvati et al.	2005/0250753 A1	11/2005	Fink et al.
2004/0087564 A1	5/2004	Wright et al.	2005/0256028 A1	11/2005	Yun et al.
2004/0089308 A1	5/2004	Welch	2005/0266078 A1	12/2005	Jorda et al.
2004/0092494 A9	5/2004	Dudley	2005/0266088 A1	12/2005	Hinrichs et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0271597 A1	12/2005	Keith
2004/0093261 A1	5/2004	Jain et al.	2005/0271598 A1	12/2005	Friedman et al.
2004/0097468 A1	5/2004	Wimalawansa	2005/0272685 A1	12/2005	Hung
2004/0101557 A1	5/2004	Gibson et al.	2005/0272712 A1	12/2005	Grubb et al.
2004/0106542 A1	6/2004	Deaver et al.	2006/0009428 A1	1/2006	Grubb et al.
2004/0110732 A1	6/2004	Masini-Eteve et al.	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0131670 A1	7/2004	Gao	2006/0018937 A1	1/2006	Friedman et al.
2004/0138103 A1	7/2004	Patt	2006/0020002 A1	1/2006	Balog
2004/0142012 A1	7/2004	Bunt et al.	2006/0030615 A1	2/2006	Salvati et al.
2004/0146539 A1	7/2004	Gupta	2006/0034889 A1	2/2006	Fensome et al.
2004/0146894 A1	7/2004	Warrington et al.	2006/0034904 A1	2/2006	Weimann
2004/0161435 A1	8/2004	Gupta	2006/0040904 A1	2/2006	Ahmed et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0176336 A1	9/2004	Rodriguez	2006/0052341 A1	3/2006	Cornish et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0069031 A1	3/2006	Loumaye
2004/0191207 A1	9/2004	Lipari et al.	2006/0078618 A1	4/2006	Constantinides et al.
2004/0191276 A1	9/2004	Muni	2006/0083778 A1	4/2006	Allison et al.
2004/0198706 A1	10/2004	Carrara et al.	2006/0084704 A1	4/2006	Shih et al.
2004/0210280 A1	10/2004	Liedtke	2006/0088580 A1	4/2006	Meconi et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0089337 A1	4/2006	Casper et al.
2004/0219124 A1	11/2004	Gupta	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0225140 A1	11/2004	Fernandez et al.	2006/0100180 A1	5/2006	Nubbemeyer et al.
2004/0234606 A1	11/2004	Levine et al.	2006/0106004 A1	5/2006	Brody et al.
2004/0241219 A1	12/2004	Hille et al.	2006/0110415 A1	5/2006	Gupta
2004/0243437 A1	12/2004	Grace et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0253319 A1	12/2004	Netke et al.	2006/0121102 A1	6/2006	Chiang
2004/0259817 A1	12/2004	Waldon et al.	2006/0121626 A1	6/2006	Imrich
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2005/0003003 A1	1/2005	Basu et al.	2006/0135619 A1	6/2006	Kick et al.
2005/0004088 A1	1/2005	Hesch	2006/0165744 A1	7/2006	Jamil et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2006/0193789 A1	8/2006	Tamarkin et al.
2005/0014729 A1	1/2005	Pulaski	2006/0194775 A1	8/2006	Tofovic et al.
2005/0020550 A1	1/2005	Morris et al.	2006/0204557 A1	9/2006	Gupta et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2006/0233743 A1	10/2006	Kelly
2005/0021009 A1	1/2005	Massara et al.	2006/0233841 A1	10/2006	Brodbeck et al.
2005/0025833 A1	2/2005	Aschkenasy et al.	2006/0235037 A1	10/2006	Purandare et al.
2005/0031651 A1	2/2005	Gervais et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0042173 A1	2/2005	Besse et al.	2006/0246122 A1	11/2006	Langguth et al.
2005/0042268 A1	2/2005	Aschkenasy et al.	2006/0247216 A1	11/2006	Haj-Yehia
2005/0048116 A1	3/2005	Straub et al.	2006/0247221 A1	11/2006	Coelingh Bennink et al.
2005/0054991 A1	3/2005	Tobyn et al.	2006/0251581 A1	11/2006	McIntyre et al.
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0252049 A1	11/2006	Shuler et al.
2005/0085453 A1	4/2005	Govindarajan	2006/0254742 A1	11/2006	Nielsen
2005/0101579 A1	5/2005	Shippen	2006/0275218 A1	12/2006	Tamarkin et al.
2005/0113350 A1	5/2005	Duesterberg et al.	2006/0275360 A1	12/2006	Ahmed et al.
2005/0118244 A1	6/2005	Theobald et al.	2006/0276414 A1	12/2006	Groenewegen et al.
2005/0118272 A1	6/2005	Besse et al.	2006/0280771 A1	12/2006	Shoichet et al.
2005/0129756 A1	6/2005	Podhaisky et al.	2006/0280797 A1	12/2006	Nagi et al.
2005/0152956 A1	7/2005	Dudley	2006/0280800 A1	12/2006	Woolfson et al.
2005/0153946 A1	7/2005	Hirsh et al.	2006/0292223 A1	12/2006	Woolfson et al.
2005/0164977 A1	7/2005	Coelingh Bennink	2007/0004693 A1	1/2007	Woolfson et al.
2005/0182105 A1	8/2005	Nirschl et al.	2007/0004694 A1	1/2007	Woolfson et al.
2005/0186141 A1	8/2005	Gonda et al.	2007/0009559 A1	1/2007	Li et al.
2005/0187267 A1	8/2005	Hamann et al.	2007/0009594 A1	1/2007	Grubb et al.
2005/0192253 A1	9/2005	Salvati et al.	2007/0010550 A1	1/2007	McKenzie
2005/0192310 A1	9/2005	Gavai et al.	2007/0014839 A1	1/2007	Bracht
2005/0196434 A1	9/2005	Brierre	2007/0015698 A1	1/2007	Kleinman et al.
2005/0207990 A1	9/2005	Funke et al.	2007/0021360 A1	1/2007	Nyce et al.
2005/0214384 A1	9/2005	Juturu et al.	2007/0027201 A1	2/2007	McComas et al.
2005/0220825 A1	10/2005	Funk et al.	2007/0031491 A1	2/2007	Levine et al.
2005/0220900 A1	10/2005	Popp et al.	2007/0037780 A1	2/2007	Ebert et al.
2005/0222106 A1	10/2005	Bracht	2007/0037782 A1	2/2007	Hibino et al.
2005/0228692 A1	10/2005	Hodgdon	2007/0042038 A1	2/2007	Besse
2005/0228718 A1	10/2005	Austin	2007/0060589 A1	3/2007	Purandare et al.
2005/0239747 A1	10/2005	Yang et al.	2007/0066628 A1	3/2007	Zhang et al.
2005/0239758 A1	10/2005	Roby	2007/0066637 A1	3/2007	Zhang et al.
2005/0244360 A1	11/2005	Billoni	2007/0066675 A1	3/2007	Zhang et al.
2005/0244522 A1	11/2005	Carrara et al.	2007/0078091 A1	4/2007	Hubles et al.
2005/0245902 A1	11/2005	Cornish et al.	2007/0088029 A1	4/2007	Balog et al.
2005/0250746 A1	11/2005	Iammatteo	2007/0093548 A1	4/2007	Diffendal et al.
2005/0250750 A1	11/2005	Cummings et al.	2007/0116729 A1	5/2007	Palepu

US 9,301,920 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2007/0167418 A1	7/2007	Ferguson	2009/0022683 A1	1/2009	Song et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0053294 A1	2/2009	Prendergast
2007/0185068 A1	8/2007	Ferguson et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0190022 A1	8/2007	Bacopoulos et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0191319 A1	8/2007	Ke et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196415 A1	8/2007	Chen et al.	2009/0081206 A1	3/2009	Leibovitz
2007/0196433 A1	8/2007	Ron et al.	2009/0081278 A1	3/2009	De Graaff et al.
2007/0207225 A1	9/2007	Squadrito	2009/0081303 A1	3/2009	Savoir et al.
2007/0225281 A1	9/2007	Zhang et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0232574 A1	10/2007	Galey et al.	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0243229 A1	10/2007	Smith et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0254858 A1	11/2007	Cronk	2009/0143344 A1	6/2009	Chang
2007/0255197 A1	11/2007	Humberstone et al.	2009/0164341 A1	6/2009	Sunvold et al.
2007/0264309 A1	11/2007	Chollet et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0264345 A1	11/2007	Eros et al.	2009/0181088 A1	7/2009	Song et al.
2007/0264349 A1	11/2007	Lee et al.	2009/0186081 A1	7/2009	Holm et al.
2007/0286819 A1	12/2007	DeVries et al.	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0287688 A1	12/2007	Chan et al.	2009/0203658 A1	8/2009	Marx et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0214474 A1	8/2009	Jennings
2007/0292359 A1	12/2007	Friedman et al.	2009/0227025 A1	9/2009	Nichols et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0227550 A1	9/2009	Mattern
2007/0292461 A1	12/2007	Tamarkin et al.	2009/0232897 A1	9/2009	Sahoo et al.
2007/0292493 A1	12/2007	Briere	2009/0258096 A1	10/2009	Cohen
2007/0298089 A1	12/2007	Saeki et al.	2009/0264395 A1	10/2009	Creasy
2008/0026035 A1	1/2008	Chollet et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0026040 A1	1/2008	Farr et al.	2009/0285772 A1	11/2009	Phasivongsa et al.
2008/0026062 A1	1/2008	Farr et al.	2009/0285869 A1	11/2009	Trimble
2008/0038219 A1	2/2008	Mosbaugh et al.	2009/0318558 A1	12/2009	Kim et al.
2008/0038350 A1	2/2008	Gerecke et al.	2009/0324714 A1	12/2009	Liu et al.
2008/0039405 A1	2/2008	Langley et al.	2009/0325916 A1	12/2009	Zhang et al.
2008/0050317 A1	2/2008	Tamarkin et al.	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0051351 A1	2/2008	Ghisalberti	2010/0028360 A1	2/2010	Atwood
2008/0063607 A1	3/2008	Tamarkin et al.	2010/0034838 A1	2/2010	Staniforth et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2010/0034880 A1	2/2010	Sintov et al.
2008/0069791 A1	3/2008	Beissert	2010/0040671 A1	2/2010	Ahmed et al.
2008/0085877 A1	4/2008	Bortz	2010/0048523 A1	2/2010	Bachman et al.
2008/0095831 A1	4/2008	McGraw	2010/0055138 A1	3/2010	Margulies et al.
2008/0095838 A1	4/2008	Abou Chakra-Vernet	2010/0074959 A1	3/2010	Hansom et al.
2008/0113953 A1	5/2008	De Vries et al.	2010/0086501 A1	4/2010	Chang et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0086599 A1	4/2010	Huempel et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0092568 A1	4/2010	Lerner et al.
2008/0125402 A1	5/2008	Dilberti	2010/0105071 A1	4/2010	Laufer et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0119585 A1	5/2010	Hille et al.
2008/0138390 A1	6/2008	Hsu et al.	2010/0129320 A1	5/2010	Phasivongsa et al.
2008/0139392 A1	6/2008	Acosta Zara et al.	2010/0136105 A1	6/2010	Chen et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0137265 A1	6/2010	Leonard
2008/0153789 A1	6/2008	Dmowski et al.	2010/0137271 A1	6/2010	Chen et al.
2008/0175814 A1	7/2008	Phasivongsa et al.	2010/0143420 A1	6/2010	Shenoy et al.
2008/0175905 A1	7/2008	Liu et al.	2010/0143481 A1	6/2010	Shenoy et al.
2008/0175908 A1	7/2008	Liu et al.	2010/0150993 A1	6/2010	Theobald et al.
2008/0188829 A1	8/2008	Creasy	2010/0152144 A1	6/2010	Hermsmeyer
2008/0206156 A1	8/2008	Cronk	2010/0168228 A1	7/2010	Bose et al.
2008/0206159 A1	8/2008	Tamarkin et al.	2010/0183723 A1	7/2010	Laurent-Applegate et al.
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0184736 A1	7/2010	Coelingh Bennink et al.
2008/0214512 A1	9/2008	Seitz et al.	2010/0190758 A1	7/2010	Fauser et al.
2008/0220069 A1	9/2008	Allison	2010/0204326 A1	8/2010	D Souza
2008/0226698 A1	9/2008	Tang et al.	2010/0210994 A1	8/2010	Zarif
2008/0227763 A1	9/2008	Lanquetin et al.	2010/0221195 A1	9/2010	Tamarkin et al.
2008/0234199 A1	9/2008	Katamreddy	2010/0227797 A1	9/2010	Axelson et al.
2008/0234240 A1	9/2008	Duesterberg et al.	2010/0240626 A1	9/2010	Kulkarni et al.
2008/0255078 A1	10/2008	Katamreddy	2010/0247482 A1	9/2010	Cui et al.
2008/0255089 A1	10/2008	Katamreddy	2010/0247632 A1	9/2010	Dong et al.
2008/0261931 A1	10/2008	Hedner et al.	2010/0247635 A1	9/2010	Rosenberg et al.
2008/0299220 A1	12/2008	Tamarkin et al.	2010/0255085 A1	10/2010	Liu et al.
2008/0306036 A1	12/2008	Katamreddy	2010/0273730 A1	10/2010	Hsu et al.
2008/0312197 A1	12/2008	Rodriguez	2010/0278759 A1	11/2010	Murad
2008/0312198 A1	12/2008	Rodriguez	2010/0279988 A1	11/2010	Setiawan et al.
2008/0319078 A1	12/2008	Katamreddy	2010/0291191 A1	11/2010	Shoichet et al.
2009/0004246 A1	1/2009	Woolfson et al.	2010/0292199 A1	11/2010	Leverd et al.
2009/0010968 A1	1/2009	Allart et al.	2010/0303825 A9	12/2010	Sirbasku
2009/0011041 A1	1/2009	Musaeva et al.	2010/0312137 A1	12/2010	Gilmour et al.
2009/0017120 A1	1/2009	Trimble et al.	2010/0316724 A1	12/2010	Whitfield et al.

US 9,301,920 B2

Page 8

(56)

References Cited**U.S. PATENT DOCUMENTS**

2010/0322884 A1	12/2010	Dipietro et al.	2012/0129773 A1	5/2012	Geier et al.
2010/0330168 A1	12/2010	Gicquel et al.	2012/0129819 A1	5/2012	Vancaillie et al.
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0136013 A1	5/2012	Li et al.
2011/0039814 A1	2/2011	Huatan et al.	2012/0142645 A1	6/2012	Marx
2011/0053845 A1	3/2011	Levine et al.	2012/0148670 A1	6/2012	Kim et al.
2011/0066473 A1	3/2011	Bernick et al.	2012/0149748 A1	6/2012	Shanler et al.
2011/0076775 A1	3/2011	Stewart et al.	2012/0172343 A1	7/2012	Lindenthal et al.
2011/0076776 A1	3/2011	Stewart et al.	2012/0184515 A1	7/2012	Klar et al.
2011/0086825 A1	4/2011	Chatroux	2012/0231052 A1	9/2012	Sitruk Ware et al.
2011/0087192 A1	4/2011	Uhland et al.	2012/0232011 A1	9/2012	Kneissel et al.
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0232042 A1	9/2012	Klar et al.
2011/0098258 A1	4/2011	Masini Eteve et al.	2012/0263679 A1	10/2012	Marlow et al.
2011/0098631 A1	4/2011	McIntyre et al.	2012/0269721 A1	10/2012	Weng et al.
2011/0104268 A1	5/2011	Pachot et al.	2012/0269878 A2	10/2012	Cantor et al.
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	2012/0277249 A1	11/2012	Andersson et al.
2011/0130372 A1	6/2011	Agostinacchio et al.	2012/0302535 A1	11/2012	Caufriez et al.
2011/0135719 A1	6/2011	Besins et al.	2012/0316130 A1	12/2012	Hendrix
2011/0142945 A1	6/2011	Chen et al.	2012/0316496 A1	12/2012	Hoffmann et al.
2011/0152840 A1	6/2011	Lee et al.	2012/0321579 A1	12/2012	Edelson et al.
2011/0158920 A1	6/2011	Morley et al.	2012/0322779 A9	12/2012	Voskuhl
2011/0171140 A1	7/2011	Illum et al.	2012/0328549 A1	12/2012	Edelson et al.
2011/0182997 A1	7/2011	Lewis et al.	2012/0329738 A1	12/2012	Liu
2011/0190201 A1	8/2011	Hyde et al.	2013/0004619 A1	1/2013	Chow et al.
2011/0195031 A1	8/2011	Du	2013/0011342 A1	1/2013	Tamarkin et al.
2011/0195114 A1	8/2011	Carrara et al.	2013/0017239 A1	1/2013	Viladot Petit et al.
2011/0195944 A1	8/2011	Mura et al.	2013/0022674 A1	1/2013	Dudley et al.
2011/0217341 A1	9/2011	Sah	2013/0023505 A1	1/2013	Garfield et al.
2011/0238003 A1	9/2011	Bruno Raimondi et al.	2013/0023823 A1	1/2013	Simpson et al.
2011/0244043 A1	10/2011	Xu et al.	2013/0028850 A1	1/2013	Tamarkin et al.
2011/0250256 A1	10/2011	Hyun Oh et al.	2013/0029947 A1	1/2013	Nachaegari et al.
2011/0250259 A1	10/2011	Buckman	2013/0029957 A1	1/2013	Giliyar et al.
2011/0250274 A1	10/2011	Shaked et al.	2013/0045266 A1	2/2013	Choi et al.
2011/0256092 A1	10/2011	Phiasivongsa et al.	2013/0045953 A1	2/2013	Sitruk Ware et al.
2011/0262373 A1	10/2011	Umbert Millet	2013/0059795 A1	3/2013	Lo et al.
2011/0262494 A1	10/2011	Achleitner et al.	2013/0064897 A1	3/2013	Binay
2011/0268665 A1	11/2011	Tamarkin et al.	2013/0072466 A1	3/2013	Choi et al.
2011/0275584 A1	11/2011	Wilckens et al.	2013/0084257 A1	4/2013	Ishida et al.
2011/0281832 A1	11/2011	Li et al.	2013/0085123 A1	4/2013	Li et al.
2011/0287094 A1	11/2011	Penhasi et al.	2013/0089574 A1	4/2013	Schmidt Gollwitzer et al.
2011/0293720 A1	12/2011	General et al.	2013/0090318 A1	4/2013	Ulmann et al.
2011/0294738 A1	12/2011	Ren et al.	2013/0102781 A1	4/2013	Bevill et al.
2011/0300167 A1	12/2011	Mcmurry et al.	2013/0108551 A1	5/2013	Langereis et al.
2011/0301087 A1	12/2011	Mcbride et al.	2013/0116215 A1	5/2013	Coma et al.
2011/0306579 A1	12/2011	Stein	2013/0116222 A1	5/2013	Arnold et al.
2011/0311592 A1	12/2011	Birbara	2013/0122051 A1	5/2013	Abidi et al.
2011/0312927 A1	12/2011	Nachaegari et al.	2013/0123175 A1	5/2013	Hill et al.
2011/0312928 A1	12/2011	Nachaegari et al.	2013/0123220 A1	5/2013	Queiroz
2011/0318405 A1	12/2011	Erwin	2013/0123351 A1	5/2013	Dewitt
2011/0318431 A1	12/2011	Gulati	2013/0129818 A1	5/2013	Bernick et al.
2012/0009276 A1	1/2012	De Grote	2013/0131027 A1	5/2013	Pakkalin et al.
2012/0015350 A1	1/2012	Nabatianyan et al.	2013/0131028 A1	5/2013	Snyder et al.
2012/0021041 A1	1/2012	Rossi et al.	2013/0131029 A1	5/2013	Bakker et al.
2012/0028888 A1	2/2012	Janz et al.	2013/0149314 A1	6/2013	Bullerdiek et al.
2012/0028910 A1	2/2012	Combal et al.	2013/0164225 A1	6/2013	Tamarkin et al.
2012/0028936 A1	2/2012	Gloge et al.	2013/0164346 A1	6/2013	Lee et al.
2012/0045532 A1	2/2012	Cohen	2013/0165744 A1	6/2013	Carson et al.
2012/0046264 A1	2/2012	Simes et al.	2013/0178452 A1	7/2013	King
2012/0046518 A1	2/2012	Yoakum et al.	2013/0183254 A1	7/2013	Zhou et al.
2012/0052077 A1	3/2012	Truitt, III et al.	2013/0183325 A1	7/2013	Bottoni et al.
2012/0058171 A1	3/2012	De Graaff et al.	2013/0189193 A1	7/2013	Tamarkin et al.
2012/0058962 A1	3/2012	Cumming et al.	2013/0189196 A1	7/2013	Tamarkin et al.
2012/0058979 A1	3/2012	Keith et al.	2013/0189230 A1	7/2013	Shoichet et al.
2012/0064135 A1	3/2012	Levin et al.	2013/0189368 A1	7/2013	Mosqueira et al.
2012/0065179 A1	3/2012	Andersson	2013/0210709 A1	8/2013	Mcmurry et al.
2012/0065221 A1	3/2012	Babul	2013/0216550 A1	8/2013	Penninger et al.
2012/0087872 A1	4/2012	Tamarkin et al.	2013/0216596 A1	8/2013	Viladot Petit et al.
2012/0101073 A1	4/2012	Mannion et al.	2013/0224177 A1	8/2013	Kim et al.
2012/0121517 A1	5/2012	Song et al.	2013/0224257 A1	8/2013	Sah et al.
2012/0121692 A1	5/2012	Xu et al.	2013/0224268 A1	8/2013	Alam et al.
2012/0122829 A1	5/2012	Taravella et al.	2013/0224300 A1	8/2013	Maggio
2012/0128625 A1	5/2012	Shalwitz et al.	2013/0225412 A1	8/2013	Sardari Lodriche et al.
2012/0128654 A1	5/2012	Terpstra et al.	2013/0225542 A1	8/2013	Poegh et al.
2012/0128683 A1	5/2012	Shantha	2013/0226113 A1	8/2013	Schumacher et al.
2012/0128733 A1	5/2012	Perrin et al.	2013/0243696 A1	9/2013	Wang et al.
2012/0128777 A1	5/2012	Keck et al.			

US 9,301,920 B2

Page 9

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2013/0245253 A1	9/2013	Marx et al.	WO	9422426 A1	3/1994	
2013/0245570 A1	9/2013	Jackson	WO	9530409 A1	11/1995	
2013/0261096 A1	10/2013	Merian et al.	WO	9609826 A2	4/1996	
2013/0266645 A1	10/2013	Becker et al.	WO	9619975	7/1996	
2013/0267485 A1	10/2013	Da Silva Maia Filho	WO	9630000 A1	10/1996	
2013/0273167 A1	10/2013	Lee et al.	WO	9705491	2/1997	
2013/0274211 A1	10/2013	Burman et al.	WO	9743989 A1	11/1997	
2013/0280213 A1	10/2013	Voskuhl	WO	9810293 A1	3/1998	
2013/0316374 A1	11/2013	Penninger et al.	WO	9832465 A1	7/1998	
2013/0317065 A1	11/2013	Tatani et al.	WO	9943304	9/1999	
2013/0317315 A1	11/2013	Lu et al.	WO	9948477 A1	9/1999	
2013/0324565 A1	12/2013	Li et al.	WO	9953910 A2	10/1999	
2013/0331363 A1	12/2013	Li et al.	WO	9963974 A2	12/1999	
2013/0338122 A1	12/2013	Bernick et al.	WO	0001351 A1	1/2000	
2013/0338124 A1	12/2013	Li et al.	WO	0006175 A1	2/2000	
2013/0345187 A1	12/2013	Rodriguez Oquendo	WO	0038659 A1	7/2000	
2014/0018335 A1	1/2014	Tatani et al.	WO	0045795 A2	8/2000	
2014/0024590 A1	1/2014	Weidhaas et al.	WO	0050007 A1	8/2000	
2014/0031289 A1	1/2014	Song et al.	WO	0059577 A1	10/2000	
2014/0031323 A1	1/2014	Perez	WO	0076522 A1	12/2000	
2014/0066416 A1	3/2014	Leunis et al.	WO	0137808 A1	5/2001	
2014/0072531 A1	3/2014	Kim et al.	WO	0154699 A1	8/2001	
2014/0079686 A1	3/2014	Barman et al.	WO	0160325 A1	8/2001	
2014/0088051 A1	3/2014	Bernick et al.	WO	0207700 A2	1/2002	
2014/0088058 A1	3/2014	Maurizio	WO	0211768 A1	2/2002	
2014/0088059 A1	3/2014	Perumal et al.	WO	0222132 A2	3/2002	
2014/0094426 A1	4/2014	Drummond et al.	WO	0240008 A2	5/2002	
2014/0094440 A1	4/2014	Bernick et al.	WO	0241878	5/2002	
2014/0094441 A1	4/2014	Bernick et al.	WO	02053131 A1	7/2002	
2014/0099362 A1	4/2014	Bernick et al.	WO	02078602 A2	10/2002	
2014/0100159 A1	4/2014	Conrad	WO	02078604 A2	10/2002	
2014/0100204 A1	4/2014	Bernick et al.	WO	03028667	4/2003	
2014/0100205 A1	4/2014	Bernick et al.	WO	03041718 A1	5/2003	
2014/0100206 A1	4/2014	Bernick et al.	WO	03041741 A1	5/2003	
2014/0113889 A1	4/2014	Connor et al.	WO	03068186 A1	8/2003	
2014/0127185 A1	5/2014	Stein et al.	WO	03077923 A1	9/2003	
2014/0127280 A1	5/2014	Duesterberg et al.	WO	03082254 A1	10/2003	
2014/0127308 A1	5/2014	Opara et al.	WO	03092588 A2	11/2003	
2014/0128798 A1	5/2014	Janson et al.	WO	2004014432	2/2004	
2014/0148491 A1	5/2014	Valia et al.	WO	2004017983 A1	3/2004	
2014/0186332 A1	7/2014	Ezrin et al.	WO	2005027911 A1	3/2004	
2014/0187487 A1	7/2014	Shoichet et al.	WO	2004032897 A2	4/2004	
2014/0193523 A1	7/2014	Henry	WO	2004052336 A2	6/2004	
2014/0194396 A1	7/2014	Li et al.	WO	2005120517 A1	6/2004	
2014/0206616 A1	7/2014	Ko et al.	WO	2004054540 A2	7/2004	
2014/0213565 A1	7/2014	Bernick et al.	WO	2004080413 A2	9/2004	
2014/0329783 A1	11/2014	Bernick et al.	WO	2005030175 A1	4/2005	
2014/0371182 A1	12/2014	Bernick et al.	WO	2005081825	9/2005	
2014/0371183 A1	12/2014	Bernick et al.	WO	2005087194 A1	9/2005	
2014/0371184 A1	12/2014	Bernick et al.	WO	2005087199 A2	9/2005	
2014/0371185 A1	12/2014	Bernick et al.	WO	2005105059 A1	11/2005	
2015/0031654 A1	1/2015	Amadio	WO	2005115335 A1	12/2005	
2015/0045335 A1	2/2015	Bernick et al.	WO	2005120470 A1	12/2005	
2015/0133421 A1	5/2015	Bernick et al.	WO	2006013369 A2	2/2006	
			WO	2006034090 A1	3/2006	
			WO	2006036899 A2	4/2006	
FOREIGN PATENT DOCUMENTS						
EP	0275716	7/1988	WO	2006053172 A2	5/2006	
EP	0622075 A1	11/1994	WO	2006105615 A1	10/2006	
EP	0785211 A1	1/1996	WO	2006113505 A2	10/2006	
EP	0785212 A1	1/1996	WO	2006138686 A1	12/2006	
EP	0811381 A1	6/1997	WO	2006138735 A2	12/2006	
EP	1094781 B1	7/2008	WO	2007045027 A1	4/2007	
EP	2191833 A1	6/2010	WO	2007103294 A2	9/2007	
GB	452238 A	8/1936	WO	2007120868	10/2007	
GB	720561	12/1954	WO	2007123790 A1	11/2007	
GB	848881 A1	9/1960	WO	2007124250 A2	11/2007	
GB	874368	8/1961	WO	2007144151 A1	12/2007	
GB	1589946	5/1981	WO	2008049516 A3	5/2008	
IN	216026	3/2008	WO	2008152444 A2	12/2008	
IN	2005KO00053	9/2009	WO	2009002542 A1	12/2008	
IN	244217	11/2010	WO	2009036311 A1	3/2009	
WO	9011064 A1	10/1990	WO	2009040818	4/2009	
WO	9317686 A1	9/1993	WO	2009069006 A2	6/2009	
			WO	2009098072 A2	8/2009	
			WO	2009133352 A2	11/2009	

US 9,301,920 B2

Page 10

(56)	References Cited	
FOREIGN PATENT DOCUMENTS		
WO	2010033188 A2	3/2010
WO	2010146872	12/2010
WO	2011000210 A1	1/2011
WO	2011073995 A2	6/2011
WO	2011120084 A1	10/2011
WO	2011128336 A1	10/2011
WO	2012009778 A2	1/2012
WO	2012024361 A1	2/2012
WO	2012055814 A1	5/2012
WO	2012055840 A1	5/2012
WO	2012065740	5/2012
WO	2012098090 A1	7/2012
WO	2012116277 A1	8/2012
WO	2012118563 A2	9/2012
WO	2012120365 A1	9/2012
WO	2012127501 A2	9/2012
WO	2012156561 A1	11/2012
WO	2012156822 A1	11/2012
WO	2012158483 A2	11/2012
WO	2012166909 A1	12/2012
WO	2012170578 A1	12/2012
WO	2013011501 A1	1/2013
WO	2013025449 A1	2/2013
WO	2013028639 A1	2/2013
WO	2013035101 A1	3/2013
WO	2013044067 A1	3/2013
WO	2013045404 A2	4/2013
WO	2013059285 A1	4/2013
WO	2013063279 A1	5/2013
WO	2013064620 A1	5/2013
WO	2013071281 A1	5/2013
WO	2013088254	6/2013
WO	2013102665 A1	7/2013
WO	2013106437 A1	7/2013
WO	2013113690	8/2013
WO	2013124415 A1	8/2013
WO	2013127727 A1	9/2013
WO	2013127728 A1	9/2013
WO	2013144356 A1	10/2013
WO	2013149258 A2	10/2013
WO	2013158454 A2	10/2013
WO	2013170052 A1	11/2013
WO	2013178587 A1	12/2013
WO	2013181449 A1	12/2013
WO	2013192248 A1	12/2013
WO	2013192249 A1	12/2013
WO	2013192250 A1	12/2013
WO	2013192251 A1	12/2013
WO	2014001904 A1	1/2014
WO	2014004424 A1	1/2014
WO	2014009434 A1	1/2014
WO	2014018569 A1	1/2014
WO	2014018570 A1	1/2014
WO	2014018571 A2	1/2014
WO	2014018856 A1	1/2014
WO	2014018932 A2	1/2014
WO	2014031958 A1	2/2014
WO	2014041120 A1	3/2014
WO	2014052792 A1	4/2014
WO	2014056897 A1	4/2014
WO	2014066442 A2	5/2014
WO	2014074846 A1	5/2014
WO	2014076231 A1	5/2014
WO	2014076569 A2	5/2014
WO	2014081598 A1	5/2014
WO	2014086739 A1	6/2014
WO	2014093114 A1	6/2014
WO	2014104784 A1	7/2014
OTHER PUBLICATIONS		
James Simon et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," <i>Obstetrics & Gynecology</i> 2008;112(5):1053-1060.		
USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.		
USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.		
USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.		
USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.		
USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.		
US 6,214,374, Apr. 10, 2001, Schmirler et al. (withdrawn).		
International Search Report and Written Opinion for related International Application No. PCT/US13/023309 mailed Apr. 9, 2013.		
International Search report for corresponding International Application No. PCT/US12/66406, mailed Jan. 24, 2013.		
Azure Pharma, Inc., "ELESTRINTM—Estradiol Gel" Drug Info, http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885 , 26 pages (Aug. 2009).		
Panchagnula et al., "Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies," <i>J Pharm Pharmacol.</i> 43(9):609-614 (Sep. 1991). Abstract Only.		
Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," <i>J. Kor. Pharm. Sci.</i> , 35(3):173-177, (2005).		
NuGen, "What is NuGen HP Hair Growth System?" http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm , (undated), 3 pages.		
NuGest 900TM, http://www.thehormoneshop.net/nugest900.htm , (undated), 4 pages.		
Tahition Noni, "Body Balance Cream," http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/ , (undated), 1 page.		
Knuth et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," <i>Advanced Drug Delivery Reviews</i> , 11 (1-2):137-167 (Jul.-Aug. 1993). Abstract Only.		
Lucy et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestral and postinsemination periods in dairy cattle," <i>Biol Reprod.</i> 35(2):300-311 (1986). Abstract Only.		
Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," <i>International Journal of Pharmaceutics</i> , 147(2):165-171 (Feb. 1997). Abstract Only.		
Diramio, "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," <i>The University of Georgia-Masters of Science Thesis</i> , 131 pages. (2004). http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1 .		
Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," <i>Drug Development and Industrial Pharmacy</i> , 35(5):525-547 (May 2009). Abstract Only.		
Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," <i>Pharmaceutical Research</i> , 21(2):201-230 (Feb. 2004). Abstract Only.		
Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," <i>Critical Reviews in Toxicology</i> , 30(3):307-345 (2000). Abstract Only.		
Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," <i>Skin Pharmacol Physiol</i> , 19:106-121 (2006). http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf .		
Committee of Obstetric Practice, Committee Opinion—No. 522, <i>Obstetrics & Gynecology</i> , 119(4):879-882 (Apr. 2012).		
Salole, "The physicochemical properties of oestradiol," <i>Journal of Pharmaceutical & Biomedical Analysis</i> , 5(7):635-648 (1987).		
Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.		
ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, <i>Obstetrics & Gynecology</i> .		
Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.		

US 9,301,920 B2

Page 11

(56)

References Cited

OTHER PUBLICATIONS

- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brandstatter-Kuhnert, M, Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, Acta, vol. 6, pp. 847-853, 1959, Univ. Innsbruck.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiolophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moleculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helveticae, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, Pharmaceutical Research, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, Journal of General Internal Medicine, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochimica Acta, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a γ-Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.

US 9,301,920 B2

Page 12

- (56) **References Cited**
- OTHER PUBLICATIONS**
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Sruhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helveticae, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: an . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PhamSciTech, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. SteroidBiochem. Mol. Biol. (2013), Elsevier.
- Wiranichapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W, Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II. vol. 1 pp. 127-139, 1968, Mikrochimica Acta.
- Kuhnert-Brandstaetter, M & Lnder, R, Zur Hydratbildung bei Steroidhormonen, Sci. Pharm., vol. 41(2) pp. 109-116, 1973.
- Kuhnert-Brandstatter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, Microchemical Journal 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, Journal of Steroid Biochemistry & Molecular Biology, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr, The WHI ten year's later: An epidemiologist's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , Jour. of Pharm. Sci., vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, Pharmaceutical Research, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, Fertility and Sterility, vol. 79(1), Jan. 2003.
- Lewis, John G, et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , Maturitas, The European Menopause Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , Steroids, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, J Thermal Anal., vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , Journal of Animal Science, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, Chemistry and Industry, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, J. Steroid Biochem. Mol.Biol. (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, J. Pharmaceutical Sciences, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , Drug Devel. & Indust. Pharmacy,35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , Clinical Endocrinology, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, Arch Pharm Res, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , European Journal of Pharmaceutics and Biopharmaceutics, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, Crystal Structure Comm., Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, Intl. Jour. of Pharma., vol. 177 pp. 231-245, 1999, Elsevier.

US 9,301,920 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/
Progynova%20TS%20100%2012%20Patches_
Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G, Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci.* 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A. E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem.Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, [http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index\[2/3/2014 1:37:50 PM\]](http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index[2/3/2014 1:37:50 PM]).
- ChemPro, Top-Notch Technology in Production of Oils and Fats, *Chempro-Edible-Oil-Refining-ISO-TUV-Austria*.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Suplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saftey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Abbas et al., Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis, *European J of Pharma*, 715 (2013) 72-75, Elsevier.
- Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceuticals substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, *Menopause: The Journal of the North American Menopause Society*, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, *Advances in Therapy®*, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, *Yale J Biology and Medicine*, vol. 35, Feb. 1963, pp. 329-340.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, *Current Medicinal Chemistry*, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, *Biology of Reproduction* 52, 1327-1333 (1995).

US 9,301,920 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductiveaged female subjects, *Fertility and Sterility*# vol. 94, No. 4, Sep. 2010, Elsevier.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, *J Clin Oncol* 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008; 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance , *Contact Dermatitis*, 71, 264-272, 2014.
- Cicinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, Mar. 2000, pp. 403-406.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," *Southern Medical Journal*, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Critchley et al., Estrogen Receptor β , But Not Estrogen Receptor α , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GmbH, 2010, 28 pages.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene based on exposure and effect data, *Contact Dermatitis* 1990; 23: 341-345.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gäfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Glaser et al, Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al, Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Herman, Anna et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, pp. 1-13.
- Hostynk, JJ, Predicting absorption of fragrance chemicals through human skin, *j. Soc.C osmeCt. hem.*,4 6, 221-229 (Jul./Aug. 1995).
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, *Journal of Cerebral Blood Flow and Metabolism* 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 α -Ethinyl Estradiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 β -Estradiol, *JPET* 290(2):740-747, 1999.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, *J Reprod Fert* (1980) 59,273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, *Environmental Health Perspectives* • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, *Contact Dermatitis*, 1992: 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, *Ann. Occup. Hyg.*, vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.
- Komm et al., Bazedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Kumasaka et al., Effects of Various Forms of Progestin on the the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2), 161-169.

US 9,301,920 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol.* Jul. 2011; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVV in OBGYN,* 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol.* May 2010; 202(5): 455.e1-455.e9.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences,* vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies,* Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA,* Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration bv'Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility,* vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy,* 2012, 3, 749-754.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Opinion on the Diethylene Glycol Momoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol.* Nov. 2008 ; 26(11): 1261-1268.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause a Systematic Review, *Obstet Gynecol* 2014;124(6)1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014;6: 139-143.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181,512-520 (2014).
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *AnnJ Obstet Gynecol.* Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010;5 943-954, Dove Press.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, *Climacteric* 2014;17:1-14.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, *Maturitas* 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, *Fertil Steril.* Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, *Toxicologic Pathology*, 42: 1188-1196,2014.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, *Journal of Experimental & Clinical Cancer Research* 2014, 33(1):41, 11 pages.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *Journal of Adolescent Health*, 2003; 32:183-186.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, *Pharmaceutical Technology*, Aug. 2014, pp. 28, 30-31.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," *Maturitas* 47 (2004) 277-283.
- Smyth et al., Summary of Toxicological Data, A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats, *Fd Cosmet. Toxicol.* vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Thereapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, *Contraception*, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause: The Journal of the North American Menopause Society*, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z., "All progestins are not created equal," *Steroids* 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" *Climacteric* 2014; 17(Suppl 2):8-11.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," *Int J Pharmaceutical Compounding*, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, *Alternative Medicine Review* vol. 12, No. 3, 2007, pp. 259-264.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, *Biology of Reproduction* 31, 399-413 (1984).

US 9,301,920 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, *Gynecol Endocrinol*, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Thomas, Peter, Characteristics of membrane progestin receptor alpha (mPR α) and progesterone membrane receptor component 1 (PGMRC1) and their roles in mediating rapid progestin actions, *Frontiers in Neuroendocrinology* 29 (2008) 292-312.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- Ueda et al., Topical and Transdermal Drug Products, *Pharmacopeial Forum*, vol. 35(3) [May-Jun. 2009], 750-754.
- U.S. Appl. No. 12/561,515 Jan. 29, 2013 Advisory Action (Opera 1.1) USPTO Final Office Action dated Oct. 26, 2012 in U.S. Appl. No. 12/561,515 (Opera 1.1).
- USPTO Notice of Allowance dated Sep. 11, 2013 in U.S. Appl. No. 12/561,515 (Opera 1.1).
- USPTO Office Action dated Dec. 12, 2011 in U.S. Appl. No. 12/561,515 (Opera 1.1).
- U.S. Appl. No. 13/843,362 Mar. 16, 2015 Restriction Requirement.
- U.S. Appl. No. 14/099,545 Jul. 14, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,562 Mar. 27, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,562 Jul. 2, 2014 Final Office Action.
- U.S. Appl. No. 14/099,562 Dec. 10, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,571 Mar. 28, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,571 Jul. 15, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,582 Apr. 29, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,582 Jun. 17, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,582 Nov. 7, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,582 Jan. 22, 2015 Notice of Allowance.
- U.S. Appl. No. 14/099,598 May 13, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,598 Jul. 3, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,598 Dec. 10, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,612 Mar. 20, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,612 Oct. 30, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,612 Nov. 26, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,623 Jul. 18, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,623 Dec. 15, 2014 Notice of Allowance.
- U.S. Appl. No. 14/103,355 Dec. 8, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/106,655 Jul. 3, 2014 Restriction Requirement.
- U.S. Appl. No. 14/125,554 Dec. 5, 2014 Restriction Requirement.
- U.S. Appl. No. 14/125,554 Apr. 14, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/136,048 Nov. 4, 2014 Restriction Requirement.
- U.S. Appl. No. 14/136,048 Mar. 12, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/475,814 Oct. 1, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/475,814 Feb. 13, 2015 Notice of Allowance.
- U.S. Appl. No. 14/475,864 Feb. 11, 2014 Notice of Allowance.
- U.S. Appl. No. 14/475,864 Oct. 2, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/476,040 Mar. 26, 2014 Restriction Requirement.
- U.S. Appl. No. 14/521,230 Dec. 5, 2014 Restriction Requirement.
- U.S. Appl. No. 14/521,230 Feb. 18, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/624,051 Apr. 7, 2015 Non-Final Office Action.
- Voegtlle et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.
- Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.
- Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role for the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).
- Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.
- Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforb.es/1LIUm1V> on Feb. 23, 2015, 3 pages.
- Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
- Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).
- Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.
- Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid.
- Fusun Acarturk, "Mucoadhesive Vaginal Drug Delivery System," *Recent Patents on Drug Delivery & Formulation*, 3(3):193-205, 2009.
- Katie O. Fuchs et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Aesthetic Dermatology*, 8(1):14-19, 2006.
- Nick Panay et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," DOI: 0.1177/1754045313489645, min.sagepub.com. Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
- Bhavnani et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," *J Clin Endocrinol Metab*. doi:10.1210/jc.2011-2492, 97(3):0000-0000, 2011, 4 pages.
- Du et al., "Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood," *Menopause: The Journal of the North American Menopause Society*, doi: 10.1097/gme.0b013e31828d39a2, 20(11):0000-0000, 2013, 7 pages.
- Patel et al., "Transdermal Drug Delivery System: A Review," *The Pharma Innovation*, 1(4):78-87, 2012.
- Sarrel et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," *American Journal of Public Health, Research and Practice*, e1-e6. doi:10.2105/AJPH.2013.301295, 2013.
- Sitruck-Ware, "Progesterins in hormonal replacement therapy: new molecules, risks, and benefits," *Menopause: The Journal of the North American Menopause Society*, 9(1):6-15, 2002.
- Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002, 13 pages.
- Bhavnani et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER α and ER β ," *Endocrinology* 2008;149(10):4857-4870.
- Hargrove et al., "Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronize Estradiol and Progesterone," *Obstetrics & Gynecology: Estrogen Replacement Therapy* 1989;73(4):606-612.
- Stanczyk et al., "Ethinyl estradiol and 17 β -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment," *Elsevier* 2013;87:706-727.
- Wood et al., "Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys," *Breast Cancer Res Treat* 2007;101:125-134.
- Fotherby, "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," *Elsevier* 1996;54:59-69.
- Kincl et al., "Increasing Oral Bioavailability of Progesterone by Formulation," *Journal of Steroid Biochemistry* 1978;9:83-84.
- Nams "Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society," *Menopause: The Journal of the North American Menopause Society* 2013;20(9):888-902.

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(56)

References Cited

OTHER PUBLICATIONS

Shufelt et al., "Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study," Menopause: The Journal of the North American Menopause Society 2013;DOI: 10.1097/GME.0b013e31829a64f9:1-7.

Sitruk-Ware et al., "Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review," Contraception 1987;36(4):373-402.

Smith et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," JAMA Internal Medicine 2013;doi:10.1001/jamainternmed.2013.11074:E1-E7.

Whitehead et al., "Absorption and metabolism of oral progesterone," British Medical Journal 1980:825-827.

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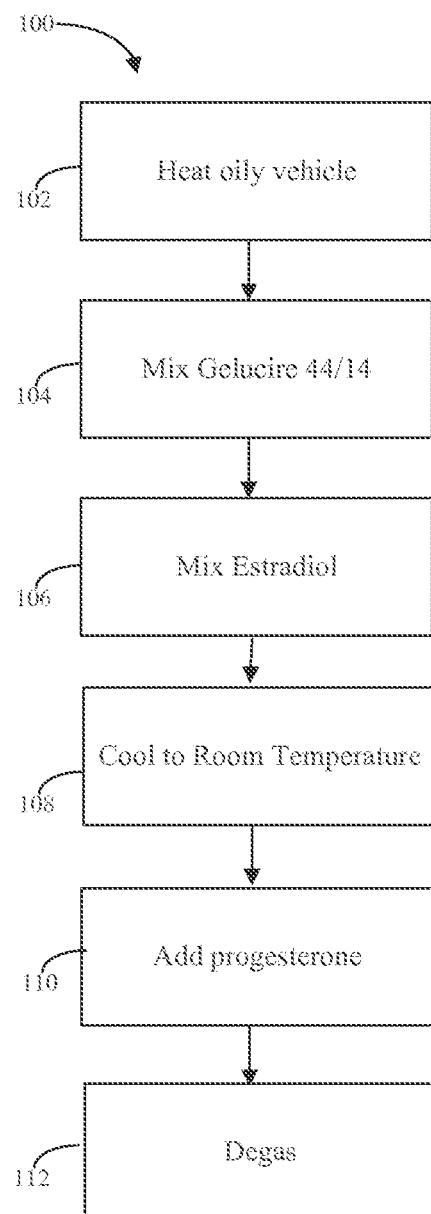
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Fig. 1

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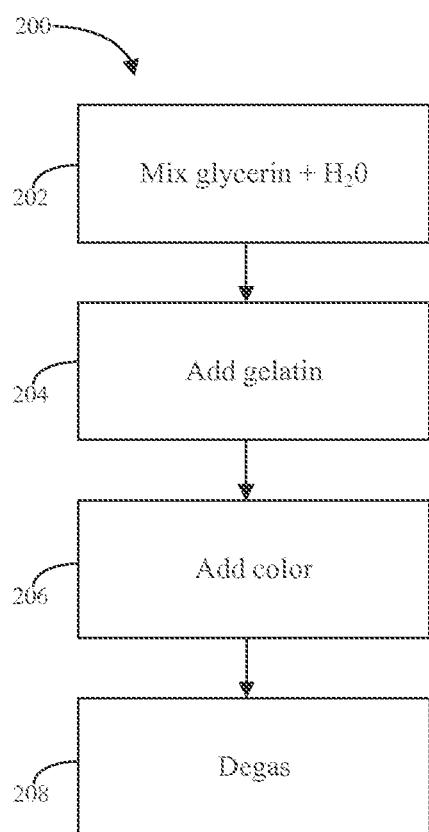


Fig. 2

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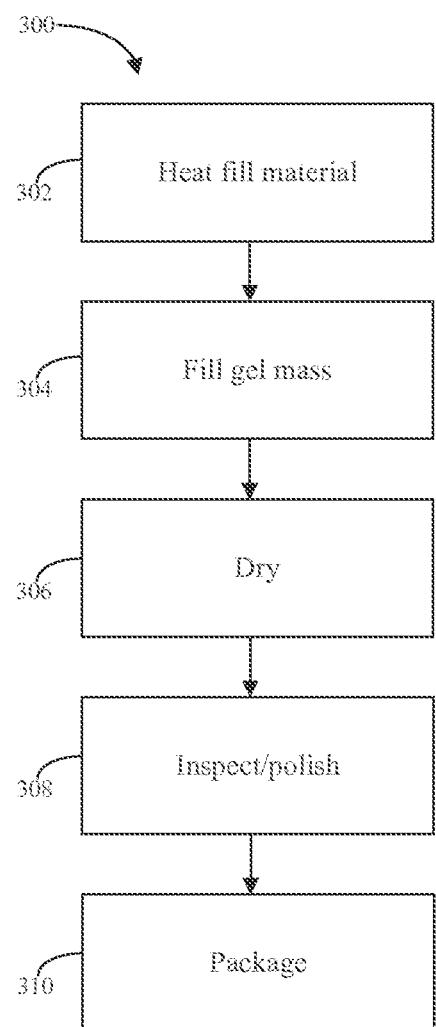
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Fig. 3

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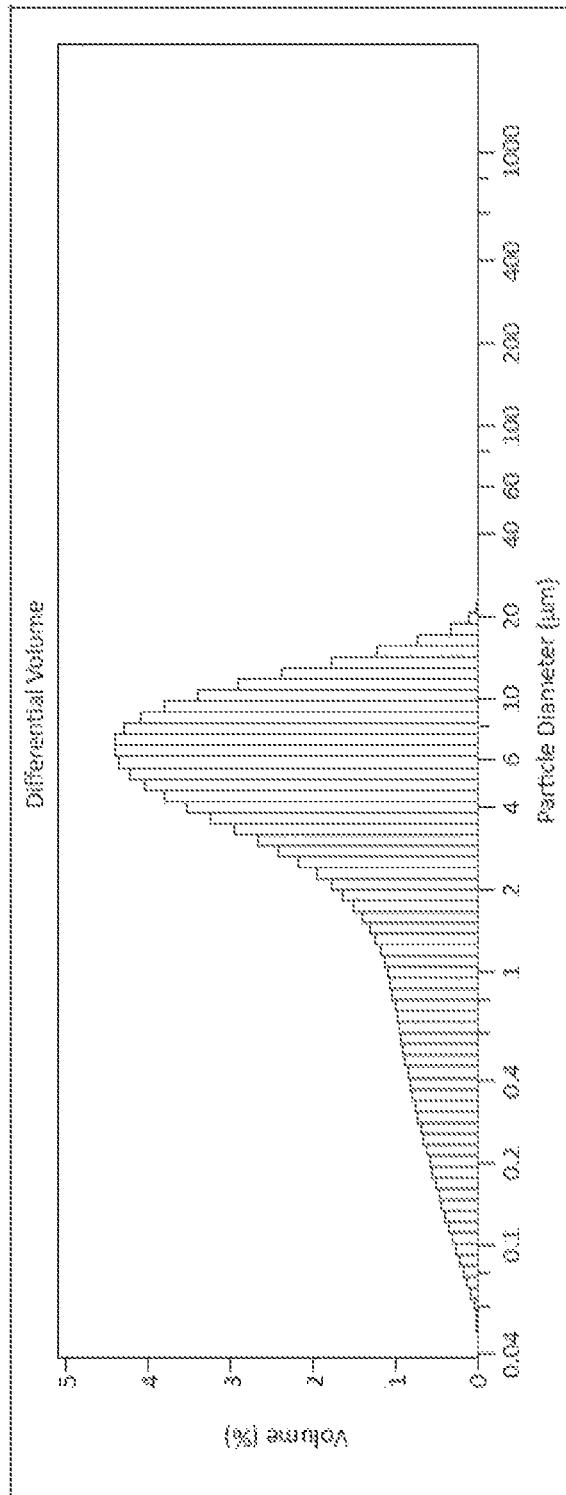


FIG. 4

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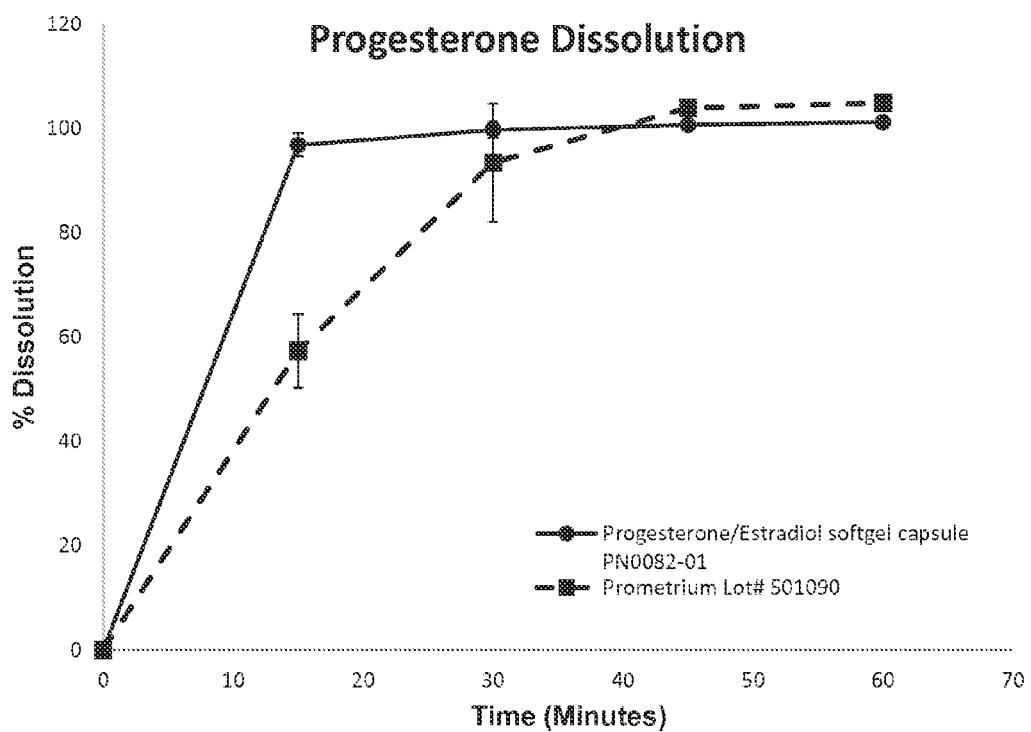


FIG. 5

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application claims priority to the following U.S. patent applications: U.S. application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES," which was filed on Nov. 21, 2012; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bod-

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ies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA # NO19781. According to the prescribing information approved for this product (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

**BRIEF DESCRIPTION OF THE
DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, "Cmax" as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, "Tmax" as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, Cmax and, optionally, Tmax are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without

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limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution, i.e., at least 98% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be

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desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Prometrium Capsules Daily Dose			
Parameter	100 mg	200 mg	300 mg
C _{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T _{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC ₀₋₁₀ (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations

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as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery

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and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol; Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

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In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50 C., e.g., at or below 50 C., at or below 40 C., or at or below 50 C. In illustrative embodiments, Gelucire 44/14 is heated to about 65 C. and Capmul MCM is heated to about 40 C. to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

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Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

	Tests				
	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monocaprylate, e.g., Capryol™ 90 (Gattefosse).

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C. in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20 C., are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40 C. or to below about 30 C., even down to room temperature.

In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

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In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

5 In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

10 Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the 15 formulation total mass.

20 In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is 25 used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and Labarafil® corn/apricot oil PEG-6 esters (Gattefosse).

30 In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

35 In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

40 In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

45 For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

50 The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

55 As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

60 As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formula-

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tions of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

Formulation A - P:50/EE:0.25:		
Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
Capmul MCM, NF	65.49	98.24
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

Formulation B - P:50/EE:0.5:		
Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
Capmul MCM, NF	65.32	97.98
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

Formulation C - P:100/EE:0.5:		
Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
Capmul MCM, NF	65.49	196.48
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

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Formulation D - P:100/EE:1:		
Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
Capmul MCM, NF	65.32	195.97
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

Formulation E - P:200/EE:2:		
Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
Capmul MCM, NF	65.32	391.94
Gelucire 44/14, NF	1.00	6.00
Total	100.00	600.00

*Note:
1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

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Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES**Example 1****Estradiol Solubility**

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference - Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in

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Miglyol;ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labrasol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

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Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

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Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

65 12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

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TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

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TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethyl ether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Myglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

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TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF	82.57	577.97	
Gelucire 44/14, NF	10.0	70.00	
TOTAL	100.00	700.00	

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/-2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone

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may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

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Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w (mg)	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxy-32- glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

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TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
	Total:	100.00	700.00	7.00	

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An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65 C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
	Total:	100.000	200.00	mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
	Total:	100.00	600.0	mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65 C. and Capmul MCM is heated to 40 C. +/- 5 C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40 C.; the mixture is then passed through a colloid mill, e.g., three times.

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Example 15

Study 352—Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP	0.30	2.07
Micronized Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout

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the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70°C. ± 20°C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters Cmax, AUC0-t & AUC0-∞ were calculated on data obtained from 24 subjects for the test product and reference product. In general, bio-availability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)					
Pharma-	Geometric Mean*		Arithmetic Mean ± Standard Deviation		
	cokinetic Parameter	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product(R)
60	C _{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
	AUC _{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
	AUC _{0-∞}	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the

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high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below for progesterone.

TABLE 19

Pharma-	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product(R)
C _{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC _{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
AUC _{0-∞}	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means.

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Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material.

Step 302 The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined

by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+-10° C. The wedge temperature may be 38° C.+-3° C. The drum cooling temperature may be 4° C.+-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about

120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

Example 17

55 Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

60 Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @ 50° C. for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

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Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C., oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

Example 18

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present dis-

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closure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as 10 illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the 15 broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

We claim:

1. A pharmaceutical formulation for administering estradiol and progesterone to a mammal in need thereof, comprising:
solubilized estradiol,
solubilized progesterone,
suspended progesterone, and
an oil,
wherein each of the solubilized estradiol, the solubilized progesterone, and the suspended progesterone is present in the oil, and
wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids.
2. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C6 to C10 fatty acids.
3. The pharmaceutical formulation of claim 1 wherein the oil is predominantly mono- and diglycerides.
4. The pharmaceutical formulation of claim 1 wherein at least 90% of the total estradiol is solubilized.
5. The pharmaceutical formulation of claim 1 further comprising a surfactant.
6. The pharmaceutical formulation of claim 5 wherein the surfactant is a non-ionic surfactant.
7. The pharmaceutical formulation of claim 6 wherein the surfactant is lauroyl polyoxy-32-glycerides.
8. The pharmaceutical formulation of claim 1 comprising:
30 to 35 wt % progesterone,
0.1 to 0.4 wt % estradiol
55 to 75 wt % of the oil, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides, and
0.5 to 10wt % non-ionic surfactant.
9. The pharmaceutical formulation of claim 8 further comprising gelatin, glycerol, and coloring agents.
10. The pharmaceutical formulation of claim 1 wherein the progesterone is released more rapidly than progesterone in peanut oil.
11. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C8 to C12 fatty acids.

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12. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C8 to C10 fatty acids.

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13. A method of treating at least one progesterone-deficient state in a mammal in need of treatment comprising administering an effective amount of a pharmaceutical formulation of claim 1.

14. A method of treating at least one estrogen-deficient state in a mammal in need of treatment comprising administering an effective amount of a pharmaceutical formulation of claim 1.

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* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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APPLICATION NO. : 13/843428

DATED : April 5, 2016

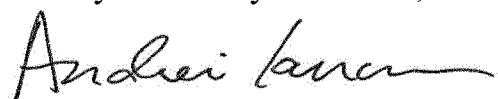
INVENTOR(S) : Brian A. Bernick et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this
Twenty-sixth Day of March, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT K



US010052386B2

(12) **United States Patent**
Bernick et al.

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(54) **PROGESTERONE FORMULATIONS**(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Julia M. Amadio**, Boca Raton, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Janice Louise Cacace**, Miami, FL (US); **Thorsteinn Thorsteinsson**, West Palm Beach, FL (US); **Frederick D. Sancilio**, Palm Beach Gardens, FL (US)(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178, and a continuation-in-part of application No. 13/843,428, filed on Mar. 15, 2013, now Pat. No. 9,301,920, and a continuation of application No. PCT/US2013/023309, filed on Jan. 25, 2013, and a continuation of application No. 13/843,362, filed on Mar. 15, 2013.

(60) Provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/662,265, filed on Jun. 20, 2012.

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(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934	Dolay
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI 1001367-9 A2	7/2012
CA	2548281 A1	6/2005

(Continued)

OTHER PUBLICATIONS

US 6,214,374, 04/2001, Schmirler et al. (withdrawn)
Abbas, M.A., et al., "Regression of Endometrial Implants Treated with Vitamin D3 in a Rat Model of Endometriosis," European Journal of Pharmacology 715(1-3):72-75, Elsevier Science, Netherlands (2013).

Abitec Corporation Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2 pages (2013).
Advisory Action dated Jan. 29, 2007 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.

Alvarez, P., et al., "Ectopic Uterine Tissue as a Chronic Pain Generator," Neuroscience 225:269-282, Elsevier Science, United States (2012).

(Continued)

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(57) **ABSTRACT**

Various pharmaceutical formulations are disclosed herein. For example, a pharmaceutical formulation is disclosed comprising ultra-micronized progesterone.

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(56)	References Cited				
U.S. PATENT DOCUMENTS					
4,008,719 A	2/1977	Theeuwes et al.	5,620,705 A	4/1997	Dong et al.
4,012,496 A	3/1977	Schopflin et al.	5,626,866 A	5/1997	Ebert et al.
4,014,334 A	3/1977	Theeuwes et al.	5,629,021 A	5/1997	Wright
4,014,987 A	3/1977	Heller et al.	5,633,011 A	5/1997	Dong et al.
4,016,251 A	4/1977	Higuchi et al.	5,633,242 A	5/1997	Oettel et al.
4,071,623 A	1/1978	van der Vies	5,639,743 A	6/1997	Kaswan et al.
4,093,709 A	6/1978	Choi et al.	5,653,983 A	8/1997	Meybeck et al.
4,154,820 A	5/1979	Simoons	5,656,286 A	8/1997	Miranda et al.
4,155,991 A	5/1979	Schopflin et al.	5,660,839 A	8/1997	Allee et al.
4,196,188 A	4/1980	Besins	5,662,927 A	9/1997	Ehrlich et al.
4,215,691 A	8/1980	Wong	5,663,160 A	9/1997	Meybeck et al.
4,237,885 A	12/1980	Wong et al.	5,663,160 A	10/1997	Lipp et al.
4,310,510 A	1/1982	Sherman et al.	5,676,968 A	10/1997	Li et al.
4,327,725 A	5/1982	Cortese et al.	5,677,292 A	10/1997	Taskovich et al.
4,372,951 A	2/1983	Vorys	5,686,097 A	11/1997	Xia et al.
4,384,096 A	5/1983	Sonnabend	5,693,335 A	12/1997	Lehtinen et al.
4,393,871 A	7/1983	Vorhauer et al.	5,694,947 A	12/1997	Hille et al.
4,402,695 A	9/1983	Wong	5,700,480 A	12/1997	Arbeit et al.
4,423,151 A	12/1983	Baranczuk	5,709,844 A	1/1998	Kanios et al.
4,449,980 A	5/1984	Millar et al.	5,719,197 A	2/1998	Caillouette
4,610,687 A	9/1986	Fogwell	5,735,801 A	4/1998	Dunn et al.
4,629,449 A	12/1986	Wong	5,739,176 A	4/1998	Bar
4,732,763 A	3/1988	Beck et al.	5,744,463 A	4/1998	Tipton et al.
4,738,957 A	4/1988	Laurent et al.	5,747,058 A	5/1998	Nargessi
4,756,907 A	7/1988	Beck et al.	5,762,614 A	6/1998	Chiang et al.
4,762,717 A	8/1988	Crowley, Jr.	5,770,176 A	6/1998	Meconi et al.
4,788,062 A	11/1988	Gale et al.	5,770,219 A	6/1998	Dong et al.
4,816,257 A	3/1989	Buster et al.	5,770,220 A	6/1998	Duclos et al.
4,822,616 A	4/1989	Zimmermann et al.	5,770,227 A	6/1998	Yewey et al.
4,865,848 A	9/1989	Cheng et al.	5,776,495 A	7/1998	Jain et al.
4,900,734 A	2/1990	Maxson et al.	5,780,044 A	7/1998	Nabahi
4,906,475 A	3/1990	Kim	5,780,050 A	8/1998	Guenther et al.
4,942,158 A	7/1990	Sarpotdar et al.	5,788,980 A	8/1998	Garfield et al.
4,961,931 A	10/1990	Wong	5,788,984 A	9/1998	Chwalisz et al.
5,030,629 A	7/1991	Rajadhyaksha	5,789,442 A	9/1998	Nakamichi et al.
5,064,654 A	11/1991	Berner et al.	5,811,416 A	10/1998	Shah
5,108,995 A	4/1992	Casper	5,811,547 A	10/1998	Burkoth et al.
5,128,138 A	7/1992	Blank	5,814,329 A	10/1998	Wille et al.
5,130,137 A	7/1992	Crowley, Jr.	5,820,878 A	10/1998	Caillouette
5,140,021 A	8/1992	Maxson et al.	5,827,200 A	10/1998	Gale et al.
5,211,952 A	5/1993	Spicer et al.	5,840,327 A	11/1998	Hirano et al.
5,252,334 A	10/1993	Chiang et al.	5,843,468 A	12/1998	Yue
5,280,023 A	1/1994	Ehrlich et al.	5,843,979 A	12/1998	Lipp et al.
5,288,496 A	2/1994	Lewis	5,858,394 A	1/1999	Lee et al.
5,340,584 A	8/1994	Spicer et al.	5,863,552 A	1/1999	Meconi et al.
5,340,585 A	8/1994	Pike et al.	5,866,603 A	3/1999	Dunn
5,340,586 A	8/1994	Pike et al.	5,882,676 A	3/1999	Carrara
5,362,497 A	11/1994	Yamada et al.	5,885,612 A	3/1999	Cummings et al.
5,382,573 A	1/1995	Casper	5,888,533 A	3/1999	Yallampalli et al.
5,393,528 A	2/1995	Staab	5,891,462 A	4/1999	Chen et al.
5,393,529 A	2/1995	Hoffmann et al.	5,891,868 A	4/1999	Plunkett et al.
5,419,910 A	5/1995	Lewis	5,902,603 A	5/1999	Lipp et al.
5,468,736 A	11/1995	Hodgen	5,904,931 A	5/1999	Farinas et al.
5,474,783 A	12/1995	Miranda et al.	5,906,830 A	5/1999	Wille et al.
5,480,776 A	1/1996	Dullien	5,912,010 A	6/1999	Caillouette
5,514,673 A	5/1996	Heckenmueller et al.	5,916,176 A	6/1999	Stewart
5,516,528 A	5/1996	Hughes et al.	RE36,247 E	7/1999	Elliesen et al.
5,527,534 A	6/1996	Myhling	5,919,477 A	7/1999	Farinas et al.
5,529,782 A	6/1996	Staab	5,922,349 A	7/1999	Ragavan et al.
5,538,736 A	7/1996	Hoffmann et al.	5,928,666 A	7/1999	Samour et al.
5,543,150 A	8/1996	Bologna et al.	5,942,243 A	8/1999	Edwards et al.
5,547,948 A	8/1996	Barcomb	5,952,000 A	9/1999	Venkateshwaran et al.
5,556,635 A	9/1996	Istin et al.	5,958,446 A	9/1999	Miranda et al.
5,565,199 A	10/1996	Page et al.	5,962,445 A	10/1999	Levine et al.
5,567,831 A	10/1996	Li	5,968,919 A	10/1999	Bon-Lapillon et al.
5,569,652 A	10/1996	Beier et al.	5,972,372 A	10/1999	Breteau et al.
5,580,572 A	12/1996	Mikler et al.	5,985,311 A	11/1999	Falk et al.
5,582,592 A	12/1996	Kendrick	5,985,850 A	11/1999	Autant et al.
5,585,370 A	12/1996	Casper	5,985,861 A	11/1999	Math et al.
5,595,759 A	1/1997	Wright et al.	5,989,568 A	11/1999	Burns
5,595,970 A	1/1997	Garfield et al.	5,993,856 A	12/1999	Caillouette
5,605,702 A	2/1997	Teillaud et al.	6,001,846 A	12/1999	Levit et al.
5,607,691 A	3/1997	Hale et al.	6,007,835 A	12/1999	Math et al.
5,607,693 A	3/1997	Bonte et al.	6,010,715 A	1/2000	Yewey et al.
5,609,617 A	3/1997	Shealy et al.	6,013,276 A	1/2000	Chen et al.

US 10,052,386 B2

Page 3

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,030,948 A	2/2000	Mann	6,451,779 B1	9/2002	Hesch	
6,039,968 A	3/2000	Nabahi	6,455,246 B1	9/2002	Howett et al.	
6,040,340 A	3/2000	Chwalisz et al.	6,455,517 B1	9/2002	Tanabe et al.	
6,056,972 A	5/2000	Hermsmeyer	6,469,016 B1	10/2002	Place et al.	
6,060,077 A	5/2000	Meignant	6,472,434 B1	10/2002	Place et al.	
6,068,853 A	5/2000	Giannos et al.	6,479,232 B1	11/2002	Howett et al.	
6,074,625 A	6/2000	Hawthorne et al.	6,495,160 B2	12/2002	Esposito et al.	
6,077,531 A	6/2000	Salin-Drouin	6,500,814 B1	12/2002	Hesch	
6,080,118 A	6/2000	Blythe	6,503,896 B1	1/2003	Tanabe et al.	
6,083,178 A	7/2000	Caillouette	6,511,969 B1	1/2003	Hermsmeyer	
6,086,916 A	7/2000	Agnus et al.	6,521,250 B2	2/2003	Meconi et al.	
6,087,352 A	7/2000	Trout	6,526,980 B1	3/2003	Tracy et al.	
6,090,404 A	7/2000	Meconi et al.	6,528,094 B1	3/2003	Savoir et al.	
6,096,338 A	8/2000	Lacy et al.	6,531,149 B1	3/2003	Kirstgen et al.	
6,106,848 A	8/2000	Preuill et al.	6,537,580 B1	3/2003	Savoir et al.	
6,117,446 A	9/2000	Place	6,538,039 B2	3/2003	Laurent	
6,117,450 A	9/2000	Dittgen et al.	6,544,196 B2	4/2003	Caillouette	
6,124,362 A	9/2000	Bradbury et al.	6,544,553 B1	4/2003	Hsia et al.	
6,133,251 A	10/2000	Dittgen et al.	6,548,053 B1	4/2003	Stewart et al.	
6,133,320 A	10/2000	Yallampalli et al.	6,548,491 B2	4/2003	Tanabe et al.	
6,139,868 A	10/2000	Hoffmann	6,551,611 B2	4/2003	Elliesen et al.	
6,139,873 A	10/2000	Hughes, Jr. et al.	6,555,131 B1	4/2003	Wolff et al.	
6,149,935 A	11/2000	Chiang et al.	6,562,367 B1	5/2003	Wolff et al.	
6,153,216 A	11/2000	Cordes et al.	6,562,370 B2	5/2003	Luo et al.	
6,165,491 A	12/2000	Grasset et al.	6,562,790 B2	5/2003	Chein et al.	
6,165,975 A	12/2000	Adams et al.	6,569,463 B2	5/2003	Patel et al.	
6,187,323 B1	2/2001	Aiache et al.	6,583,129 B1	6/2003	Mazer et al.	
6,187,339 B1	2/2001	de Haan et al.	6,586,006 B2	7/2003	Roser et al.	
6,190,331 B1	2/2001	Caillouette	6,589,549 B2	7/2003	Shin et al.	
6,201,072 B1	3/2001	Rathi et al.	6,593,317 B1	7/2003	de Ziegler et al.	
6,217,886 B1	4/2001	Önyüksel et al.	6,599,519 B1	7/2003	Seo et al.	
6,225,297 B1	5/2001	Stockemann et al.	6,610,652 B2	8/2003	Adams et al.	
6,227,202 B1	5/2001	Matapurkar	6,610,670 B2	8/2003	Backensfeld et al.	
6,228,383 B1	5/2001	Hansen et al.	6,610,674 B1	8/2003	Schreiber	
6,228,852 B1	5/2001	Shaak	6,635,274 B1	10/2003	Masiz et al.	
6,242,509 B1	6/2001	Berger et al.	6,638,528 B1	10/2003	Kanios	
6,245,811 B1	6/2001	Horrobin et al.	6,638,536 B2	10/2003	Savoir et al.	
6,262,115 B1	7/2001	Guittard et al.	6,645,528 B1	11/2003	Straub et al.	
6,264,980 B1	7/2001	Hille	6,649,155 B1	11/2003	Dunlop et al.	
6,267,984 B1	7/2001	Beste et al.	6,653,298 B2	11/2003	Potter et al.	
6,274,165 B1	8/2001	Meconi et al.	6,656,929 B1	12/2003	Agnus et al.	
6,277,418 B1	8/2001	Marakverich et al.	6,660,726 B2	12/2003	Hill et al.	
6,283,927 B1	9/2001	Caillouette	6,663,608 B2	12/2003	Rathbone et al.	
6,287,588 B1	9/2001	Shih et al.	6,663,895 B2	12/2003	Savoir et al.	
6,287,693 B1	9/2001	Savoir et al.	6,682,757 B1	1/2004	Wright	
6,294,188 B1	9/2001	Ragavan et al.	6,692,763 B1	2/2004	Cummings et al.	
6,294,192 B1	9/2001	Patel et al.	6,708,822 B1	3/2004	Muni	
6,294,550 B1	9/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.	
6,299,900 B1	10/2001	Reed et al.	6,737,081 B2	5/2004	Savoir et al.	
6,303,132 B1	10/2001	Nelson	6,740,333 B2	5/2004	Beckett et al.	
6,303,588 B1	10/2001	Danielov	6,743,448 B2	6/2004	Kryger	
6,306,841 B1	10/2001	Place et al.	6,743,815 B2	6/2004	Huebner et al.	
6,306,914 B1	10/2001	de Ziegler et al.	6,747,018 B2	6/2004	Tanabe et al.	
6,309,669 B1	10/2001	Setterstrom et al.	6,750,291 B2	6/2004	Kim et al.	
6,309,848 B1	10/2001	Howett et al.	6,756,208 B2	6/2004	Griffin et al.	
6,312,703 B1	11/2001	Orthoefer	6,776,164 B2	8/2004	Bunt et al.	
6,328,987 B1	12/2001	Marini	6,787,152 B2	9/2004	Kirby et al.	
6,342,491 B1	1/2002	Dey et al.	6,805,877 B2	10/2004	Massara et al.	
6,344,211 B1	2/2002	Hille	6,809,085 B1	10/2004	Elson et al.	
6,372,209 B1	4/2002	Chrisope	6,818,226 B2	11/2004	Reed et al.	
6,372,245 B1	4/2002	Bowman et al.	6,821,524 B2	11/2004	Marini	
6,372,246 B1	4/2002	Wei et al.	6,841,716 B1	1/2005	Tsutsumi	
6,387,390 B1	5/2002	Deaver et al.	6,844,334 B2	1/2005	Hill et al.	
6,402,705 B1	6/2002	Caillouette	6,855,703 B1	2/2005	Hill et al.	
6,416,778 B1	7/2002	Ragavan et al.	6,860,859 B2	3/2005	Mehrotra et al.	
6,420,352 B1	7/2002	Knowles	6,866,865 B2	3/2005	Hsia et al.	
6,423,039 B1	7/2002	Rathbone et al.	6,869,969 B2	3/2005	Heubner et al.	
6,423,683 B1	7/2002	Heaton et al.	6,878,518 B2	4/2005	Whitehead	
6,432,438 B1	8/2002	Shukla	6,901,278 B1	5/2005	Notelovitz	
6,436,633 B1	8/2002	Kreider et al.	6,905,705 B2	6/2005	Palm et al.	
6,440,454 B1	8/2002	Santoro et al.	6,911,211 B2	6/2005	Eini et al.	
6,444,224 B1	9/2002	Rathbone et al.	6,911,438 B2	6/2005	Wright	
6,444,234 B1	9/2002	Kirby et al.	6,923,988 B2	8/2005	Patel et al.	
6,451,300 B1	9/2002	Dunlop et al.	6,924,274 B2	8/2005	Lardy et al.	
6,451,339 B2	9/2002	Patel et al.	6,932,983 B1	8/2005	Straub et al.	

US 10,052,386 B2

Page 4

(56)

References Cited**U.S. PATENT DOCUMENTS**

6,939,558	B2	9/2005	Massara et al.	7,732,408	B2	6/2010	Josephson et al.
6,943,021	B2	9/2005	Klausner et al.	7,749,989	B2	7/2010	Hill et al.
6,958,327	B1	10/2005	Hillisch et al.	7,767,656	B2	8/2010	Shoichet et al.
6,960,337	B2	11/2005	Daniels et al.	7,799,769	B2	9/2010	White et al.
6,962,691	B1	11/2005	Lulla et al.	7,815,936	B2	10/2010	Hasenzahl et al.
6,962,908	B2	11/2005	Aloba et al.	7,815,949	B2	10/2010	Cohen
6,967,194	B1	11/2005	Matsuo et al.	7,829,115	B2	11/2010	Besins et al.
6,974,569	B2	12/2005	Dunlop et al.	7,829,116	B2	11/2010	Griswold et al.
6,977,250	B2	12/2005	Rodriguez	RE42,012	E	12/2010	Deaver et al.
6,978,945	B2	12/2005	Wong et al.	7,850,992	B2	12/2010	Kim et al.
6,995,149	B1	2/2006	Endrikat et al.	7,854,753	B2	12/2010	Kraft et al.
7,004,321	B1	2/2006	Palm et al.	7,858,607	B2	12/2010	Mamchur
7,005,429	B2	2/2006	Dey et al.	RE42,072	E	1/2011	Deaver et al.
7,011,846	B2	3/2006	Shojaei et al.	7,862,552	B2	1/2011	McIntyre et al.
7,018,992	B2	3/2006	Koch et al.	7,867,990	B2	1/2011	Schultz et al.
7,030,104	B2	4/2006	Gray et al.	7,871,643	B2	1/2011	Lizio et al.
7,030,157	B2	4/2006	Ke et al.	7,879,830	B2	2/2011	Wiley
RE39,104	E	5/2006	Duclos et al.	7,884,093	B2	2/2011	Creasy et al.
7,074,779	B2	7/2006	Sui et al.	7,925,519	B2	4/2011	Greene
7,083,590	B1	8/2006	Bunt et al.	7,939,104	B2	5/2011	Barbera et al.
7,091,213	B2	8/2006	Metcalf, III et al.	7,943,602	B2	5/2011	Bunschoten et al.
7,094,228	B2	8/2006	Zhang et al.	7,943,604	B2	5/2011	Coelingh Bennink et al.
7,097,853	B1	8/2006	Garbe et al.	7,945,459	B2	5/2011	Grace et al.
7,101,342	B1	9/2006	Caillouette	7,960,368	B2	6/2011	Nickisch et al.
7,105,573	B2	9/2006	Krajcik et al.	7,989,436	B2	8/2011	Hill et al.
7,135,190	B2	11/2006	Piao et al.	7,989,487	B2	8/2011	Welsh et al.
7,153,522	B1	12/2006	Ikeura et al.	8,022,053	B2	9/2011	Mueller et al.
7,163,681	B2	1/2007	Giles-Komar et al.	8,048,017	B2	11/2011	Xu
7,163,699	B2	1/2007	Besse	8,048,869	B2	11/2011	Bunschoten et al.
7,175,850	B2	2/2007	Cevc	8,063,030	B2	11/2011	Ellman
7,179,799	B2	2/2007	Hill et al.	8,071,576	B2	12/2011	Coelingh Bennink et al.
7,196,074	B2	3/2007	Blye et al.	8,071,729	B2	12/2011	Giles-Komar et al.
7,198,800	B1	4/2007	Ko	8,075,916	B2	12/2011	Song et al.
7,198,801	B2	4/2007	Carrara et al.	8,075,917	B2	12/2011	Chung et al.
7,226,910	B2	6/2007	Wilson et al.	8,076,317	B2	12/2011	Kulmann
7,247,625	B2	7/2007	Zhang et al.	8,076,319	B2	12/2011	Leonard
7,250,446	B2	7/2007	Sangita et al.	8,080,553	B2	12/2011	Keith et al.
7,267,829	B2	9/2007	Kirby et al.	8,088,605	B2	1/2012	Beaudet et al.
7,300,926	B2	11/2007	Prokai et al.	8,096,940	B2	1/2012	Josephson et al.
7,303,763	B2	12/2007	Ho	8,101,209	B2	1/2012	Legrand et al.
7,317,037	B2	1/2008	Fensome et al.	8,101,773	B2	1/2012	Smith et al.
7,329,654	B2	2/2008	Kanojia et al.	8,114,152	B2	2/2012	Furst
7,335,650	B2	2/2008	Potter et al.	8,114,434	B2	2/2012	Sasaki et al.
7,374,779	B2	5/2008	Chen et al.	8,114,442	B2	2/2012	Tucker et al.
7,378,404	B2	5/2008	Peters et al.	8,119,741	B2	2/2012	Pavlín
7,381,427	B2	6/2008	Ancira et al.	8,121,886	B2	2/2012	Azar
7,388,006	B2	6/2008	Schmees et al.	8,124,118	B2	2/2012	Lennernas et al.
7,387,789	B2	7/2008	Klose et al.	8,124,595	B2	2/2012	Boissonneault
7,414,043	B2	8/2008	Kosemund et al.	8,147,561	B2	4/2012	Binmoeller
7,427,413	B2	9/2008	Savoir et al.	8,148,546	B2	4/2012	Schuster et al.
7,427,609	B2	9/2008	Leonard	8,158,613	B2	4/2012	Staniforth et al.
7,429,576	B2	9/2008	Labrie	8,158,614	B2	4/2012	Lambert et al.
7,431,941	B2	10/2008	Besins et al.	8,163,722	B2	4/2012	Savoir et al.
7,456,159	B2	11/2008	Houze et al.	8,177,449	B2	5/2012	Bayly et al.
7,459,445	B2	12/2008	Hill et al.	8,182,833	B2	5/2012	Hermsmeyer
7,465,587	B2	12/2008	Imrich	8,187,615	B2	5/2012	Friedman
7,470,433	B2	12/2008	Carrara et al.	8,195,403	B2	6/2012	Ishikawa et al.
7,485,666	B2	2/2009	Villanueva et al.	8,202,736	B2	6/2012	Mousa et al.
7,497,855	B2	3/2009	Ausiello et al.	8,217,024	B2	7/2012	Ahmed et al.
7,498,303	B2	3/2009	Arnold et al.	8,221,785	B2	7/2012	Chien
7,534,765	B2	5/2009	Gregg et al.	8,222,008	B2	7/2012	Thoene
7,534,780	B2	5/2009	Wyrwa et al.	8,222,237	B2	7/2012	Nickisch et al.
7,550,142	B2	6/2009	Giles-Komar et al.	8,227,454	B2	7/2012	Hill et al.
7,563,565	B1	7/2009	Matsuo et al.	8,227,509	B2	7/2012	Castro et al.
7,569,274	B2	8/2009	Besse et al.	8,241,664	B2	8/2012	Dudley et al.
7,572,779	B2	8/2009	Aloba et al.	8,247,393	B2	8/2012	Ahmed et al.
7,572,780	B2	8/2009	Hermsmeyer	8,257,724	B2	9/2012	Cromack et al.
7,589,082	B2	9/2009	Savoir et al.	8,257,725	B2	9/2012	Cromack et al.
7,671,027	B2	3/2010	Loumaye	8,268,352	B2	9/2012	Vaya et al.
7,674,783	B2	3/2010	Hermsmeyer	8,268,806	B2	9/2012	Labrie
7,687,281	B2	3/2010	Roth et al.	8,268,878	B2	9/2012	Armer et al.
7,687,485	B2	3/2010	Levinson et al.	8,273,730	B2	9/2012	Fernandez et al.
7,694,683	B2	4/2010	Callister et al.	8,287,888	B2	10/2012	Song et al.
7,704,983	B1	4/2010	Hodgen et al.	8,288,366	B2	10/2012	Chochinov et al.
7,727,720	B2	6/2010	Dhallan	8,318,898	B2	11/2012	Fasel et al.
				8,324,193	B2	12/2012	Lee-Sepsick et al.
				8,329,680	B2	12/2012	Evans et al.
				8,337,814	B2	12/2012	Osbakken et al.
				8,344,007	B2	1/2013	Tang et al.

US 10,052,386 B2

Page 5

(56)	References Cited				
U.S. PATENT DOCUMENTS					
8,349,820 B2	1/2013 Zeun et al.	2001/0005728 A1	6/2001	Guittard et al.	
8,353,863 B2	1/2013 Imran	2001/0009673 A1	7/2001	Lipp et al.	
8,357,723 B2	1/2013 Satyam	2001/0021816 A1	9/2001	Caillouette	
8,361,995 B2	1/2013 Schramm	2001/0023261 A1	9/2001	Ryoo et al.	
8,362,091 B2	1/2013 Tamarkin et al.	2001/0027189 A1	10/2001	Bennink et al.	
8,372,424 B2	2/2013 Berry et al.	2001/0029357 A1	10/2001	Bunt et al.	
8,372,806 B2	2/2013 Bohler et al.	2001/0031747 A1	10/2001	deZiegler et al.	
8,377,482 B2	2/2013 Laurie et al.	2001/0032125 A1	10/2001	Bhan et al.	
8,377,994 B2	2/2013 Gray et al.	2001/0034340 A1	10/2001	Pickar	
8,394,759 B2	3/2013 Barathur et al.	2001/0053383 A1	12/2001	Miranda et al.	
8,435,561 B2	3/2013 Besins et al.	2001/0056068 A1	12/2001	Chwalisz et al.	
8,415,332 B2	4/2013 Diliberti et al.	2002/0012710 A1	1/2002	Lansky	
8,420,111 B2	4/2013 Hermsmeyer	2002/0026158 A1	2/2002	Rathbone et al.	
8,435,972 B2	5/2013 Stein et al.	2002/0028788 A1	3/2002	Bunt et al.	
8,449,879 B2	5/2013 Laurent-Applegate et al.	2002/0035070 A1	3/2002	Gardlik et al.	
8,450,108 B2	5/2013 Boyce	2002/0058648 A1	5/2002	Hammerly	
8,454,945 B2	6/2013 McCook et al.	2002/0058926 A1	5/2002	Rathbone et al.	
8,455,468 B2	6/2013 Hoffman et al.	2002/0064541 A1	5/2002	Lapidot et al.	
8,461,138 B2	6/2013 Boissonneault	2002/0076441 A1	6/2002	Shin et al.	
8,476,252 B2	7/2013 Achleitner et al.	2002/0102308 A1	8/2002	Wei et al.	
8,481,488 B2	7/2013 Carter	2002/0107230 A1	8/2002	Waldon et al.	
8,486,374 B2	7/2013 Tamarkin et al.	2002/0114803 A1	8/2002	Deaver et al.	
8,486,442 B2	7/2013 Matsushita et al.	2002/0119174 A1	8/2002	Gardlik et al.	
8,492,368 B2	7/2013 Vanlandingham et al.	2002/0119198 A1	8/2002	Gao et al.	
8,507,467 B2	8/2013 Matsui et al.	2002/0132801 A1	9/2002	Heil et al.	
8,512,693 B2	8/2013 Capito et al.	2002/0137749 A1	9/2002	Levinson et al.	
8,512,754 B2	8/2013 Needham	2002/0142017 A1	10/2002	Simonnet	
8,518,376 B2	8/2013 Tamarkin et al.	2002/0151530 A1	10/2002	Leonard et al.	
8,536,159 B2	9/2013 Li et al.	2002/0156394 A1	10/2002	Mehrotra et al.	
8,540,967 B2	9/2013 Barrett et al.	2002/0169150 A1	11/2002	Pickar	
8,541,400 B2	9/2013 Johnsson et al.	2002/0169205 A1	11/2002	Chwalisz et al.	
8,551,462 B2	10/2013 Goldstein et al.	2002/0173510 A1	11/2002	Levinson et al.	
8,557,281 B2	10/2013 Halliday et al.	2002/0193356 A1	12/2002	Van Beek et al.	
8,568,374 B2	10/2013 De Graaff et al.	2002/0193758 A1	12/2002	Sandberg	
8,591,951 B2	11/2013 Kohn et al.	2002/0197286 A1	12/2002	Brandman et al.	
8,613,951 B2	12/2013 Zale et al.	2003/0003139 A1	1/2003	Lipp et al.	
8,633,178 B2	1/2014 Bernick et al.	2003/0004145 A1	1/2003	Leonard	
8,633,180 B2	1/2014 Li et al.	2003/0007994 A1	1/2003	Bunt et al.	
8,636,787 B2	1/2014 Sabaria	2003/0027772 A1	2/2003	Breton	
8,636,982 B2	1/2014 Tamarkin et al.	2003/0044453 A1	3/2003	Dittgen et al.	
8,653,129 B2	2/2014 Fein et al.	2003/0049307 A1	3/2003	Gyurik	
8,658,627 B2	2/2014 Voskuhl	2003/0064097 A1	4/2003	Patel et al.	
8,658,628 B2	2/2014 Baucom	2003/0064975 A1	4/2003	Koch et al.	
8,663,681 B2	3/2014 Nakamichi et al.	2003/0078245 A1	4/2003	Sirbasku	
8,663,692 B1	3/2014 Mueller et al.	2003/0091620 A1	5/2003	Fikstad et al.	
8,663,703 B2	3/2014 Lerner et al.	2003/0091640 A1	5/2003	Ramanathan et al.	
8,664,207 B2	3/2014 Li et al.	2003/0092691 A1	5/2003	Besse et al.	
8,669,293 B2	3/2014 Levy et al.	2003/0096012 A1	5/2003	Besse et al.	
8,679,552 B2	3/2014 Gutheray	2003/0104048 A1	6/2003	Patel et al.	
8,694,358 B2	4/2014 Tryfon	2003/0109507 A1	6/2003	Franke et al.	
8,697,127 B2	4/2014 Sah	2003/0113268 A1	6/2003	Buenafae et al.	
8,697,710 B2	4/2014 Li et al.	2003/0114420 A1	6/2003	Salvati et al.	
8,703,105 B2	4/2014 Tamarkin et al.	2003/0114430 A1	6/2003	MacLeod et al.	
8,709,385 B2	4/2014 Tamarkin et al.	2003/0124182 A1	7/2003	Shojaei et al.	
8,709,451 B2	4/2014 Rapoport et al.	2003/0124191 A1	7/2003	Besse et al.	
8,715,735 B2	5/2014 Funke et al.	2003/0130558 A1	7/2003	Massara et al.	
8,721,331 B2	5/2014 Raghuprasad	2003/0144258 A1	7/2003	Heil et al.	
8,722,021 B2	5/2014 Friedman et al.	2003/0157157 A1	8/2003	Luo et al.	
8,734,846 B2	5/2014 Ali et al.	2003/0166509 A1	9/2003	Edwards et al.	
8,735,381 B2	5/2014 Podolski	2003/0170295 A1	9/2003	Kim et al.	
8,741,336 B2	6/2014 Dipierro et al.	2003/0175329 A1	9/2003	Azarnoff et al.	
8,741,373 B2	6/2014 Bromley et al.	2003/0175333 A1	9/2003	Shefer et al.	
8,753,661 B2	6/2014 Steinmuller-Nethl et al.	2003/0180352 A1	9/2003	Patel et al.	
8,784,882 B2	7/2014 Mattern	2003/0181353 A1	9/2003	Nyce	
8,815,261 B2	8/2014 Hanma	2003/0181728 A1	9/2003	Salvati et al.	
8,846,648 B2	9/2014 Bernick et al.	2003/0191096 A1	10/2003	Leonard et al.	
8,846,649 B2	9/2014 Bernick et al.	2003/0195177 A1	10/2003	Leonard et al.	
8,933,059 B2	1/2015 Bernick et al.	2003/0215496 A1	11/2003	Patel et al.	
8,987,237 B2	3/2015 Bernick et al.	2003/0219402 A1	11/2003	Rutter	
8,987,238 B2	3/2015 Bernick et al.	2003/0220297 A1	11/2003	Berstein et al.	
8,993,548 B2	3/2015 Bernick et al.	2003/0224057 A1	12/2003	Martin-Letellier et al.	
8,993,549 B2	3/2015 Bernick et al.	2003/0224059 A1	12/2003	Lerner et al.	
9,006,222 B2	4/2015 Bernick et al.	2003/0225047 A1	12/2003	Caubel et al.	
9,012,434 B2	4/2015 Bernick et al.	2003/0225048 A1	12/2003	Caubel et al.	
9,289,382 B2	3/2016 Bernick et al.	2003/0225050 A1	12/2003	Eichardt et al.	

US 10,052,386 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2003/0228686 A1	12/2003	Klausner et al.	2005/0192253 A1	9/2005	Salvati et al.
2003/0229057 A1	12/2003	Caubel et al.	2005/0192310 A1	9/2005	Gavai et al.
2003/0235596 A1	12/2003	Gao et al.	2005/0196434 A1	9/2005	Briere
2003/0236236 A1	12/2003	Chen et al.	2005/0207990 A1	9/2005	Funke et al.
2004/0009960 A1	1/2004	Heil et al.	2005/0209209 A1	9/2005	Koch et al.
2004/0022820 A1	2/2004	Anderson	2005/0214384 A1	9/2005	Juturu et al.
2004/0034001 A1	2/2004	Karara	2005/0220825 A1	10/2005	Funke et al.
2004/0037881 A1	2/2004	Guittard et al.	2005/0220900 A1	10/2005	Popp et al.
2004/0039356 A1	2/2004	Maki et al.	2005/0222106 A1	10/2005	Bracht
2004/0043043 A1	3/2004	Schlyter et al.	2005/0228692 A1	10/2005	Hodgdon
2004/0043943 A1	3/2004	Guittard et al.	2005/0228718 A1	10/2005	Austin
2004/0044080 A1	3/2004	Place et al.	2005/0239747 A1	10/2005	Yang et al.
2004/0048900 A1	3/2004	Flood	2005/0239758 A1	10/2005	Roby
2004/0052824 A1	3/2004	Abou Chakra-Vernet et al.	2005/0244360 A1	11/2005	Billoni
2004/0073024 A1	4/2004	Metcalf, III et al.	2005/0244522 A1	11/2005	Carrara et al.
2004/0077605 A1	4/2004	Salvati et al.	2005/0245902 A1	11/2005	Cornish et al.
2004/0077606 A1	4/2004	Salvati et al.	2005/0250746 A1	11/2005	Iammatteo
2004/0087548 A1	5/2004	Salvati et al.	2005/0250750 A1	11/2005	Cummings et al.
2004/0087564 A1	5/2004	Wright et al.	2005/0250753 A1	11/2005	Fink et al.
2004/0089308 A1	5/2004	Welch	2005/0256028 A1	11/2005	Yun et al.
2004/0092494 A9	5/2004	Dudley	2005/0266078 A1	12/2005	Jorda et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0266088 A1	12/2005	Hinrichs et al.
2004/0093261 A1	5/2004	Jain et al.	2005/0271597 A1	12/2005	Keith
2004/0097468 A1	5/2004	Wimalawansa	2005/0271598 A1	12/2005	Friedman et al.
2004/0101557 A1	5/2004	Gibson et al.	2005/0272685 A1	12/2005	Hung
2004/0106542 A1	6/2004	Deaver et al.	2005/0272712 A1	12/2005	Grubb et al.
2004/0110732 A1	6/2004	Masini-Eteve et al.	2006/0009428 A1	1/2006	Grubb et al.
2004/0131670 A1	7/2004	Gao	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0138103 A1	7/2004	Patt	2006/0018937 A1	1/2006	Friedman et al.
2004/0142012 A1	7/2004	Bunt et al.	2006/0019978 A1	1/2006	Balog
2004/0146539 A1	7/2004	Gupta	2006/0020002 A1	1/2006	Salvati et al.
2004/0146894 A1	7/2004	Warrington et al.	2006/0030615 A1	2/2006	Fensome et al.
2004/0161435 A1	8/2004	Gupta	2006/0034889 A1	2/2006	Jo et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0034904 A1	2/2006	Weimann
2004/0176336 A1	9/2004	Rodriguez	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0052341 A1	3/2006	Cornish et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0069031 A1	3/2006	Loumaye
2004/0191276 A1	9/2004	Muni	2006/0078618 A1	4/2006	Constantinides et al.
2004/0198706 A1	10/2004	Carrara et al.	2006/0083778 A1	4/2006	Allison et al.
2004/0210280 A1	10/2004	Liedtke	2006/0084704 A1	4/2006	Shih et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0088580 A1	4/2006	Meconi et al.
2004/0219124 A1	11/2004	Gupta	2006/0089337 A1	4/2006	Casper et al.
2004/0225140 A1	11/2004	Fernandez et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0234606 A1	11/2004	Levine et al.	2006/0100180 A1	5/2006	Nubbemeyer et al.
2004/0241219 A1	12/2004	Hille et al.	2006/0106004 A1	5/2006	Brody et al.
2004/0243437 A1	12/2004	Grace et al.	2006/0110415 A1	5/2006	Gupta
2004/0253319 A1	12/2004	Netke et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0259817 A1	12/2004	Waldon et al.	2006/0121102 A1	6/2006	Chiang
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0121626 A1	6/2006	Imrich
2005/0003003 A1	1/2005	Basu et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2005/0004088 A1	1/2005	Hesch	2006/0135619 A1	6/2006	Kick et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2006/0165744 A1	7/2006	Jamil et al.
2005/0014729 A1	1/2005	Pulaski	2006/0193789 A1	8/2006	Tamarkin et al.
2005/0020550 A1	1/2005	Morris et al.	2006/0194775 A1	8/2006	Tofovic et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2006/0204557 A1	9/2006	Gupta et al.
2005/0021009 A1	1/2005	Massara et al.	2006/0233743 A1	10/2006	Kelly
2005/0025833 A1	2/2005	Aschkenasy et al.	2006/0233841 A1	10/2006	Brodbeck et al.
2005/0031651 A1	2/2005	Gervais et al.	2006/0235037 A1	10/2006	Purandare et al.
2005/0042173 A1	2/2005	Besse et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0042268 A1	2/2005	Aschkenasy et al.	2006/0246122 A1	11/2006	Langguth et al.
2005/0048116 A1	3/2005	Straub et al.	2006/0247216 A1	11/2006	Haj-Yehia
2005/0054991 A1	3/2005	Tobyn et al.	2006/0247221 A1	11/2006	Coelingh Bennink et al.
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0251581 A1	11/2006	McIntyre et al.
2005/0085453 A1	4/2005	Govindarajan	2006/0252049 A1	11/2006	Shuler et al.
2005/0101579 A1	5/2005	Shippen	2006/0257472 A1	11/2006	Neilsen
2005/0113350 A1	5/2005	Duesterberg et al.	2006/0275218 A1	12/2006	Tamarkin et al.
2005/0118244 A1	6/2005	Theobald et al.	2006/0275360 A1	12/2006	Ahmed et al.
2005/0118272 A1	6/2005	Besse et al.	2006/0276414 A1	12/2006	Coelingh Bennink et al.
2005/0129756 A1	6/2005	Podhaisky et al.	2006/0280771 A1	12/2006	Groenewegen et al.
2005/0152956 A1	7/2005	Dudley	2006/0280797 A1	12/2006	Shoichet et al.
2005/0153946 A1	7/2005	Hirsh et al.	2006/0280800 A1	12/2006	Nagi et al.
2005/0164977 A1	7/2005	Coelingh Bennink	2006/0292223 A1	12/2006	Woolfson et al.
2005/0182105 A1	8/2005	Nirschl et al.	2007/0004693 A1	1/2007	Woolfson et al.
2005/0186141 A1	8/2005	Gonda et al.	2007/0004694 A1	1/2007	Woolfson et al.
2005/0187267 A1	8/2005	Hamann et al.	2007/0009559 A1	1/2007	Li et al.
			2007/0009594 A1	1/2007	Grubb et al.
			2007/0010550 A1	1/2007	McKenzie
			2007/0014839 A1	1/2007	Bracht
			2007/0015698 A1	1/2007	Kleinman et al.

US 10,052,386 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2007/0021360 A1	1/2007	Nyce et al.	2008/0220069 A1	9/2008	Allison
2007/0027201 A1	2/2007	McComas et al.	2008/0226698 A1	9/2008	Tang et al.
2007/0031491 A1	2/2007	Levine et al.	2008/0227763 A1	9/2008	Lanquetin et al.
2007/0037780 A1	2/2007	Ebert et al.	2008/0234199 A1	9/2008	Katamreddy
2007/0037782 A1	2/2007	Hibino et al.	2008/0234240 A1	9/2008	Duesterberg et al.
2007/0042038 A1	2/2007	Besse	2008/0255078 A1	10/2008	Katamreddy
2007/0060589 A1	3/2007	Purandare et al.	2008/0255089 A1	10/2008	Katamreddy
2007/0066628 A1	3/2007	Zhang et al.	2008/0261931 A1	10/2008	Hedner et al.
2007/0066637 A1	3/2007	Zhang et al.	2008/0299220 A1	12/2008	Tamarkin et al.
2007/0066675 A1	3/2007	Zhang et al.	2008/0306036 A1	12/2008	Katamreddy
2007/0078091 A1	4/2007	Hubler et al.	2008/0312197 A1	12/2008	Rodriguez
2007/0088029 A1	4/2007	Balog et al.	2008/0312198 A1	12/2008	Rodriguez
2007/0093548 A1	4/2007	Diffendal et al.	2008/0319078 A1	12/2008	Katamreddy
2007/0116729 A1	5/2007	Palepu	2009/0004246 A1	1/2009	Woolfson et al.
2007/0116829 A1	5/2007	Prakash et al.	2009/0010968 A1	1/2009	Allart et al.
2007/0128263 A1	6/2007	Gargiulo et al.	2009/0011041 A1	1/2009	Musaeva et al.
2007/0154533 A1	7/2007	Dudley	2009/0017120 A1	1/2009	Trimble et al.
2007/0167418 A1	7/2007	Ferguson	2009/0022683 A1	1/2009	Song et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0053294 A1	2/2009	Prendergast
2007/0185068 A1	8/2007	Ferguson et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0190022 A1	8/2007	Bacopoulos et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0191319 A1	8/2007	Ke et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196415 A1	8/2007	Chen et al.	2009/0074859 A1	3/2009	Patel
2007/0196433 A1	8/2007	Ron et al.	2009/0081206 A1	3/2009	Leibovitz
2007/0207225 A1	9/2007	Squadrito	2009/0081278 A1	3/2009	De Graaff et al.
2007/0225281 A1	9/2007	Zhang et al.	2009/0081303 A1	3/2009	Savoir et al.
2007/0232574 A1	10/2007	Galey et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0093440 A1	4/2009	Murad
2007/0243229 A1	10/2007	Smith et al.	2009/0098069 A1	4/2009	Vacca
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0099106 A1	4/2009	Phasivongsa et al.
2007/0254858 A1	11/2007	Cronk	2009/0099149 A1	4/2009	Liu et al.
2007/0255197 A1	11/2007	Humberstone et al.	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0264309 A1	11/2007	Chollet et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0264345 A1	11/2007	Eros et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0264349 A1	11/2007	Lee et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0286819 A1	12/2007	DeVries et al.	2009/0143344 A1	6/2009	Chang
2007/0287688 A1	12/2007	Chan et al.	2009/0164341 A1	6/2009	Sunvold et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0292359 A1	12/2007	Friedman et al.	2009/0181088 A1	7/2009	Song et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0186081 A1	7/2009	Holm et al.
2007/0292461 A1	12/2007	Tamarkin et al.	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0292493 A1	12/2007	Briere	2009/0203658 A1	8/2009	Marx et al.
2007/0298089 A1	12/2007	Saeki et al.	2009/0214474 A1	8/2009	Jennings
2008/0026035 A1	1/2008	Chollet et al.	2009/0227025 A1	9/2009	Nichols et al.
2008/0026040 A1	1/2008	Farr et al.	2009/0227550 A1	9/2009	Mattern
2008/0026062 A1	1/2008	Farr et al.	2009/0232897 A1	9/2009	Sahoo et al.
2008/0038219 A1	2/2008	Mosbaugh et al.	2009/0258096 A1	10/2009	Cohen
2008/0038350 A1	2/2008	Gerecke et al.	2009/0264395 A1	10/2009	Creasy
2008/0039405 A1	2/2008	Langley et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0050317 A1	2/2008	Tamarkin et al.	2009/0285772 A1	11/2009	Phasivongsa et al.
2008/0051351 A1	2/2008	Ghisalberti	2009/0285869 A1	11/2009	Trimble
2008/0063607 A1	3/2008	Tamarkin et al.	2009/0318558 A1	12/2009	Kim et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2009/0324714 A1	12/2009	Liu et al.
2008/0069791 A1	3/2008	Beissert	2009/0325916 A1	12/2009	Zhang et al.
2008/0085877 A1	4/2008	Bortz	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0095831 A1	4/2008	McGraw	2010/0028360 A1	2/2010	Atwood
2008/0095838 A1	4/2008	Abou Chakra-Vernet	2010/0034838 A1	2/2010	Staniforth et al.
2008/0113953 A1	5/2008	De Vries et al.	2010/0034880 A1	2/2010	Sintov et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0040671 A1	2/2010	Ahmed et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0048523 A1	2/2010	Bachman et al.
2008/0125402 A1	5/2008	Dilberti	2010/0055138 A1	3/2010	Margulies et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0074959 A1	3/2010	Hansom et al.
2008/0138390 A1	6/2008	Hsu et al.	2010/0086501 A1	4/2010	Chang et al.
2008/0139392 A1	6/2008	Acosta-Zara et al.	2010/0086599 A1	4/2010	Huempel et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0092568 A1	4/2010	Lerner et al.
2008/0153789 A1	6/2008	Dmowski et al.	2010/0105071 A1	4/2010	Laufer et al.
2008/0175814 A1	7/2008	Phasivongsa et al.	2010/0119585 A1	5/2010	Hille et al.
2008/0175905 A1	7/2008	Liu et al.	2010/0129320 A1	5/2010	Phasivongsa et al.
2008/0175908 A1	7/2008	Liu et al.	2010/0136105 A1	6/2010	Chen et al.
2008/0188829 A1	8/2008	Creasy	2010/0137265 A1	6/2010	Leonard
2008/0206156 A1	8/2008	Cronk	2010/0137271 A1	6/2010	Chen et al.
2008/0206159 A1	8/2008	Tamarkin et al.	2010/0143420 A1	6/2010	Shenoy et al.
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0143481 A1	6/2010	Shenoy et al.
2008/0214512 A1	9/2008	Seitz et al.	2010/0150993 A1	6/2010	Theobald et al.
			2010/0152144 A1	6/2010	Hermsmeyer
			2010/0168228 A1	7/2010	Bose et al.
			2010/0183723 A1	7/2010	Laurent-Applegate et al.
			2010/0184736 A1	7/2010	Coelingh Bennink et al.

US 10,052,386 B2

Page 8

(56)	References Cited				
U.S. PATENT DOCUMENTS					
2010/0190758 A1	7/2010 Fauser et al.	2012/0046518 A1	2/2012 Yoakum et al.		
2010/0204326 A1	8/2010 D'Souza	2012/0052077 A1	3/2012 Truitt, III et al.		
2010/0210994 A1	8/2010 Zarif	2012/0058171 A1	3/2012 De Graaff et al.		
2010/0221195 A1	9/2010 Tamarkin et al.	2012/0058962 A1	3/2012 Cumming et al.		
2010/0227797 A1	9/2010 Axelson et al.	2012/0058979 A1	3/2012 Keith et al.		
2010/0240626 A1	9/2010 Kulkarni et al.	2012/0064135 A1	3/2012 Levin et al.		
2010/0247482 A1	9/2010 Cui et al.	2012/0065179 A1	3/2012 Andersson		
2010/0247632 A1	9/2010 Dong et al.	2012/0065221 A1	3/2012 Babul		
2010/0247635 A1	9/2010 Rosenberg et al.	2012/0087872 A1	4/2012 Tamarkin et al.		
2010/0255085 A1	10/2010 Liu et al.	2012/0101073 A1	4/2012 Mannion et al.		
2010/0273730 A1	10/2010 Hsu et al.	2012/0121517 A1	5/2012 Song et al.		
2010/0278759 A1	11/2010 Murad	2012/0121692 A1	5/2012 Xu et al.		
2010/0279988 A1	11/2010 Setiawan et al.	2012/0122829 A1	5/2012 Taravella et al.		
2010/0291191 A1	11/2010 Shoichet et al.	2012/0128625 A1	5/2012 Shalwitz et al.		
2010/0292199 A1	11/2010 Leverd et al.	2012/0128654 A1	5/2012 Terpstra et al.		
2010/0303825 A9	12/2010 Sirbasku	2012/0128683 A1	5/2012 Shantha		
2010/0312137 A1	12/2010 Gilmour et al.	2012/0128733 A1	5/2012 Perrin et al.		
2010/0316724 A1	12/2010 Whitfield et al.	2012/0128777 A1	5/2012 Keck et al.		
2010/0322884 A1	12/2010 Dipietro et al.	2012/0129773 A1	5/2012 Geier et al.		
2010/0330168 A1	12/2010 Gicquel et al.	2012/0129819 A1	5/2012 Vancaillie et al.		
2011/0028439 A1	2/2011 Witt-Enderby et al.	2012/0136013 A1	5/2012 Li et al.		
2011/0039814 A1	2/2011 Huatan et al.	2012/0142645 A1	6/2012 Marx		
2011/0053845 A1	3/2011 Levine et al.	2012/0148670 A1	6/2012 Kim et al.		
2011/0066473 A1	3/2011 Bernick et al.	2012/0149748 A1	6/2012 Shanler et al.		
2011/0076775 A1	3/2011 Stewart et al.	2012/0172343 A1	7/2012 Lindenthal et al.		
2011/0076776 A1	3/2011 Stewart et al.	2012/0184515 A1	7/2012 Klar et al.		
2011/0086825 A1	4/2011 Chatroux	2012/0231052 A1	9/2012 Sitruk-Ware et al.		
2011/0087192 A1	4/2011 Uhland et al.	2012/0232011 A1	9/2012 Kneissel et al.		
2011/0091555 A1	4/2011 De Luigi Bruschi et al.	2012/0232042 A1	9/2012 Klar et al.		
2011/0098258 A1	4/2011 Masini-Eteve et al.	2012/0263679 A1	10/2012 Marlow et al.		
2011/0098631 A1	4/2011 McIntyre et al.	2012/0269721 A1	10/2012 Weng et al.		
2011/0104268 A1	5/2011 Pachot et al.	2012/0269878 A2	10/2012 Cantor et al.		
2011/0104289 A1	5/2011 Savoir Vilboeuf et al.	2012/0277249 A1	11/2012 Andersson et al.		
2011/0130372 A1	6/2011 Agostinacchio et al.	2012/0277727 A1	11/2012 Doshi et al.		
2011/0135719 A1	6/2011 Besins et al.	2012/0283671 A1	11/2012 Shibata et al.		
2011/0142945 A1	6/2011 Chen et al.	2012/0295911 A1	11/2012 Mannion et al.		
2011/0152840 A1	6/2011 Lee et al.	2012/0301517 A1	11/2012 Zhang et al.		
2011/0158920 A1	6/2011 Morley et al.	2012/0301538 A1	11/2012 Gordon-Beresford et al.		
2011/0171140 A1	7/2011 Illum et al.	2012/0302535 A1	11/2012 Caufriez et al.		
2011/0182997 A1	7/2011 Lewis et al.	2012/0316130 A1	12/2012 Hendrix		
2011/0190201 A1	8/2011 Hyde et al.	2012/0316496 A1	12/2012 Hoffmann et al.		
2011/0195031 A1	8/2011 Du	2012/0321579 A1	12/2012 Edelson et al.		
2011/0195114 A1	8/2011 Carrara et al.	2012/0322779 A9	12/2012 Voskuhl		
2011/0195944 A1	8/2011 Mura et al.	2012/0328549 A1	12/2012 Edelson et al.		
2011/0217341 A1	9/2011 Sah	2012/0329738 A1	12/2012 Liu		
2011/0238003 A1	9/2011 Bruno-Raimondi et al.	2013/0004619 A1	1/2013 Chow et al.		
2011/0244043 A1	10/2011 Xu et al.	2013/0011342 A1	1/2013 Tamarkin et al.		
2011/0250256 A1	10/2011 Hyun-Oh et al.	2013/0017239 A1	1/2013 Viladot Petit et al.		
2011/0250259 A1	10/2011 Buckman	2013/0022674 A1	1/2013 Dudley et al.		
2011/0250274 A1	10/2011 Shaked et al.	2013/0023505 A1	1/2013 Garfield et al.		
2011/0256092 A1	10/2011 Phasivongsa et al.	2013/0023823 A1	1/2013 Simpson et al.		
2011/0262373 A1	10/2011 Umbert Millet	2013/0028850 A1	1/2013 Tamarkin et al.		
2011/0262494 A1	10/2011 Achleitner et al.	2013/0029947 A1	1/2013 Nachaegari et al.		
2011/0268665 A1	11/2011 Tamarkin et al.	2013/0029957 A1	1/2013 Giliyar et al.		
2011/0275584 A1	11/2011 Wilckens et al.	2013/0045266 A1	2/2013 Choi et al.		
2011/0281832 A1	11/2011 Li et al.	2013/0045953 A1	2/2013 Sitruk-Ware et al.		
2011/0287094 A1	11/2011 Penhasi et al.	2013/0059795 A1	3/2013 Lo et al.		
2011/0293720 A1	12/2011 General et al.	2013/0064897 A1	3/2013 Binay		
2011/0294738 A1	12/2011 Ren et al.	2013/0072466 A1	3/2013 Choi et al.		
2011/0300167 A1	12/2011 McMurry et al.	2013/0084257 A1	4/2013 Ishida et al.		
2011/0301087 A1	12/2011 McBride et al.	2013/0085123 A1	4/2013 Li et al.		
2011/0306579 A1	12/2011 Stein	2013/0085974 A1	4/2013 Schmidt-Gollwitzer et al.		
2011/0311592 A1	12/2011 Birbara	2013/0090318 A1	4/2013 Ullmann et al.		
2011/0312927 A1	12/2011 Nachaegari et al.	2013/0102781 A1	4/2013 Bevill et al.		
2011/0312928 A1	12/2011 Nachaegari et al.	2013/0108551 A1	5/2013 Langereis et al.		
2011/0318405 A1	12/2011 Erwin	2013/0116215 A1	5/2013 Coma et al.		
2011/0318431 A1	12/2011 Gulati	2013/0116222 A1	5/2013 Arnold et al.		
2012/0009276 A1	1/2012 De Groot	2013/0122051 A1	5/2013 Abidi et al.		
2012/0015350 A1	1/2012 Nabatianyan et al.	2013/0123175 A1	5/2013 Hill et al.		
2012/0021041 A1	1/2012 Rossi et al.	2013/0123220 A1	5/2013 Queiroz		
2012/0028888 A1	2/2012 Janz et al.	2013/0123351 A1	5/2013 Dewitt		
2012/0028910 A1	2/2012 Combal et al.	2013/0129818 A1	5/2013 Bernick et al.		
2012/0028936 A1	2/2012 Gloger et al.	2013/0131027 A1	5/2013 Pakkalin et al.		
2012/0045532 A1	2/2012 Cohen	2013/0131028 A1	5/2013 Snyder et al.		
2012/0046264 A1	2/2012 Simes et al.	2013/0131029 A1	5/2013 Bakker et al.		
		2013/0149314 A1	6/2013 Bullerdiek et al.		
		2013/0164225 A1	6/2013 Tamarkin et al.		
		2013/0164346 A1	6/2013 Lee et al.		
		2013/0165744 A1	6/2013 Carson et al.		

US 10,052,386 B2

Page 9

(56)	References Cited		2015/0133421 A1	5/2015	Bernick et al.
U.S. PATENT DOCUMENTS		2015/0196640 A1	7/2015	Cacace et al.	
		2015/0202211 A1	7/2015	Amadio et al.	
		2017/0340739 A1	11/2017	Cacace et al.	
2013/0178452 A1	7/2013	King	CA 2856520 A1	5/2013	
2013/0183254 A1	7/2013	Zhou et al.	CN 102258455	11/2011	
2013/0183325 A1	7/2013	Bottoni et al.	CN 102258455 A	11/2011	
2013/0189193 A1	7/2013	Tamarkin et al.	EP 0275716 A1	7/1988	
2013/0189196 A1	7/2013	Tamarkin et al.	EP 0622075 A1	11/1994	
2013/0189230 A1	7/2013	Shoichet et al.	EP 0785211 A1	1/1996	
2013/0189368 A1	7/2013	Mosqueira et al.	EP 0785212 A1	1/1996	
2013/0210709 A1	8/2013	McMurry et al.	EP 0811381 A1	6/1997	
2013/0216550 A1	8/2013	Penninger et al.	EP 0785211 A1	7/1997	
2013/0216596 A1	8/2013	Viladot Petit et al.	EP 0785212 A1	7/1997	
2013/0224177 A1	8/2013	Kim et al.	EP 1094781 B1	7/2006	
2013/0224257 A1	8/2013	Sah et al.	EP 2191833 A1	6/2010	
2013/0224268 A1	8/2013	Alam et al.	EP 2191833 B1	2/2013	
2013/0224300 A1	8/2013	Maggio	EP 0811381 B1	5/2003	
2013/0225412 A1	8/2013	Sardari Lodriche et al.	EP 1094781 B1	7/2006	
2013/0225542 A1	8/2013	Poegh et al.	EP 2191833 A1	6/2010	
2013/0226113 A1	8/2013	Schumacher et al.	EP 2191833 B1	2/2013	
2013/0243696 A1	9/2013	Wang et al.	GB 452238 A	8/1936	
2013/0245253 A1	9/2013	Marx et al.	GB 720561	12/1954	
2013/0245570 A1	9/2013	Jackson	GB 720561 A	12/1954	
2013/0261096 A1	10/2013	Merian et al.	GB 848881 A	9/1960	
2013/0266645 A1	10/2013	Becker et al.	GB 874368	8/1961	
2013/0267485 A1	10/2013	Da Silva Maia Filho	GB 874368 A	8/1961	
2013/0273167 A1	10/2013	Lee et al.	GB 1589946 A	5/1981	
2013/0274211 A1	10/2013	Burman et al.	IN 216026	3/2008	
2013/0280213 A1	10/2013	Voskuhl	IN 2005KO00053	9/2009	
2013/0316374 A1	11/2013	Penninger et al.	IN 244217	11/2010	
2013/0317065 A1	11/2013	Tatani et al.	JP 2007-516259 A	6/2007	
2013/0317315 A1	11/2013	Lu et al.	JP 2009-510127 A	3/2009	
2013/0324565 A1	12/2013	Li et al.	MX 2014/0006256 A	10/2014	
2013/0331363 A1	12/2013	Li et al.	WO 1990011064 A1	10/1990	
2013/0338122 A1	12/2013	Bernick et al.	WO 1993017686 A1	9/1993	
2013/0338123 A1	12/2013	Bernick et al.	WO 1994022426 A1	3/1994	
2013/0338124 A1	12/2013	Li et al.	WO 1995030409 A1	11/1995	
2013/0345187 A1	12/2013	Rodríguez Oquendo	WO 1996009826 A2	4/1996	
2014/0018335 A1	1/2014	Tatani et al.	WO WO-9619975 A1	7/1996	
2014/0024590 A1	1/2014	Weidhaas et al.	WO 1996030000 A1	10/1996	
2014/0031289 A1	1/2014	Song et al.	WO 9705491	2/1997	
2014/0031323 A1	1/2014	Perez	WO 1997043989 A1	11/1997	
2014/0066416 A1	3/2014	Leunis et al.	WO 1998010293 A1	3/1998	
2014/0072531 A1	3/2014	Kim et al.	WO 1998032465 A1	7/1998	
2014/0079686 A1	3/2014	Barman et al.	WO 1998051280 A1	11/1998	
2014/0088051 A1	3/2014	Bernick et al.	WO 1999039700 A1	2/1999	
2014/0088058 A1	3/2014	Maurizio	WO 1999032072 A1	7/1999	
2014/0088059 A1	3/2014	Perumal et al.	WO 1999039700 A1	8/1999	
2014/0094426 A1	4/2014	Drummond et al.	WO 1999042109 A1	8/1999	
2014/0094440 A1	4/2014	Bernick et al.	WO 9943304	9/1999	
2014/0094441 A1	4/2014	Bernick et al.	WO 1999048477 A1	9/1999	
2014/0099362 A1	4/2014	Bernick et al.	WO 1999053910 A2	10/1999	
2014/0100159 A1	4/2014	Conrad	WO 2000038659 A1	11/1999	
2014/0100204 A1	4/2014	Bernick et al.	WO 1999063974 A2	12/1999	
2014/0100205 A1	4/2014	Bernick et al.	WO 2000001351 A1	1/2000	
2014/0100206 A1	4/2014	Bernick et al.	WO 2000006175 A1	2/2000	
2014/0113889 A1	4/2014	Connor et al.	WO 2000045795 A2	8/2000	
2014/0127185 A1	5/2014	Stein et al.	WO 2000050007 A1	8/2000	
2014/0127280 A1	5/2014	Duesterberg et al.	WO 2000059577 A1	10/2000	
2014/0127308 A1	5/2014	Opara et al.	WO 2001037808 A1	11/2000	
2014/0128798 A1	5/2014	Janson et al.	WO 2000076522 A1	12/2000	
2014/0148491 A1	5/2014	Valia et al.	WO 2002007700 A2	7/2001	
2014/0186332 A1	7/2014	Ezrin et al.	WO 2001054699 A1	8/2001	
2014/0187487 A1	7/2014	Shoichet et al.	WO 2001060325 A1	8/2001	
2014/0193523 A1	7/2014	Henry	WO 2002011768 A1	2/2002	
2014/0194396 A1	7/2014	Li et al.	WO 2002022132 A2	3/2002	
2014/0206616 A1	7/2014	Ko et al.	WO 2002040008 A2	5/2002	
2014/0213565 A1	7/2014	Bernick et al.	WO WO-0241878 A2	5/2002	
2014/0288035 A1	9/2014	Hubner et al.	WO 2002053131 A1	7/2002	
2014/0329783 A1	11/2014	Bernick et al.	WO 2002078602 A3	2/2003	
2014/0335193 A1	11/2014	Rintoul et al.	WO WO-03028667 A2	4/2003	
2014/0370084 A1	12/2014	Bernick et al.	WO 2003041718 A1	5/2003	
2014/0371182 A1	12/2014	Bernick et al.	WO 2003041741 A1	5/2003	
2014/0371183 A1	12/2014	Bernick et al.	WO 2003068186 A1	8/2003	
2014/0371184 A1	12/2014	Bernick et al.	WO 2003077923 A1	9/2003	
2014/0371185 A1	12/2014	Bernick et al.	WO 2003082254 A1	10/2003	
2015/0031654 A1	1/2015	Amadio	WO 2002078604 A3	11/2003	
2015/0045335 A1	2/2015	Bernick et al.	WO 2003092588 A2	11/2003	

US 10,052,386 B2

Page 10

(56)	References Cited							
FOREIGN PATENT DOCUMENTS								
WO	WO-2004014397	A1	2/2004	WO	WO-2013035101	A1		
WO	WO-2004014432	A1	2/2004	WO	WO-2013044067	A1		
WO	2004017983	A1	3/2004	WO	WO-2013045404	A2		
WO	2005027911	A1	3/2004	WO	WO-2013059285	A1		
WO	2004032897	A2	4/2004	WO	WO-2013078422	A2		
WO	2004052336	A2	6/2004	WO	WO-2013063279	A1		
WO	2005120517	A1	6/2004	WO	WO-2013064620	A1		
WO	2004054540	A2	7/2004	WO	WO-2013071281	A1		
WO	2004080413	A2	9/2004	WO	WO-2013088254	A1		
WO	2005030175	A1	4/2005	WO	WO-2013102665	A1		
WO	2005087194	A1	9/2005	WO	WO-2013106437	A1		
WO	2005087199	A2	9/2005	WO	WO-2013113690	A1		
WO	WO-2005081825	A2	9/2005	WO	WO-2013124415	A1		
WO	2005105059	A1	11/2005	WO	WO-2013127727	A1		
WO	2005115335	A1	12/2005	WO	WO-2013127728	A1		
WO	2005120470	A1	12/2005	WO	WO-2013144356	A1		
WO	2005120517	A1	12/2005	WO	WO-2013149258	A2		
WO	2006013369	A2	2/2006	WO	WO-2013158454	A2		
WO	2006034090	A1	3/2006	WO	WO-2013170052	A1		
WO	2006036899	A2	4/2006	WO	2013192248	A1		
WO	2006053172	A2	5/2006	WO	2013192249	A1		
WO	2006105615	A1	10/2006	WO	2013192250	A1		
WO	2006113505	A2	10/2006	WO	2013192251	A1		
WO	2006138686	A1	12/2006	WO	WO-2013178587	A1		
WO	2006138735	A2	12/2006	WO	WO-2013181449	A1		
WO	2007045027	A1	4/2007	WO	WO-2014001904	A1		
WO	WO-2007/038796	A1	4/2007	WO	WO-2014004424	A1		
WO	2007103294	A2	9/2007	WO	WO-2014009434	A1		
WO	2006138735	A3	10/2007	WO	WO-2014018569	A1		
WO	WO-2007120868	A2	10/2007	WO	WO-2014018570	A1		
WO	2007123790	A1	11/2007	WO	WO-2014018571	A2		
WO	2007124250	A2	11/2007	WO	WO-2014018856	A1		
WO	2007124250	A3	12/2007	WO	WO-2014018932	A2		
WO	2007144151	A1	12/2007	WO	WO-2014031958	A1		
WO	2007103294	A3	4/2008	WO	WO-2014041120	A1		
WO	2008049516	A3	5/2008	WO	WO-2014052792	A1		
WO	2008049516	A3	6/2008	WO	WO-2014056897	A1		
WO	2008152444	A2	12/2008	WO	WO-2014066442	A2		
WO	2009002542	A1	12/2008	WO	WO-2014074846	A1		
WO	2009036311	A1	3/2009	WO	WO-2014076231	A1		
WO	2009040818		4/2009	WO	WO-2014076569	A2		
WO	2008152444	A3	6/2009	WO	WO-2014081598	A1		
WO	2009069006	A2	6/2009	WO	WO-2014086739	A1		
WO	2009098072	A2	8/2009	WO	WO-2014093114	A1		
WO	2009098072	A3	10/2009	WO	WO-2014104784	A1		
WO	2009133352	A2	11/2009	OTHER PUBLICATIONS				
WO	2009069006	A3	12/2009	Application Note JASCO CD Spectra of Pharmaceuticals Substances Steroids, 2 pages.				
WO	2010033188	A2	3/2010	Archer, D.F., et al., "Effects of Ospemifene on the Female Reproductive and Urinary Tracts : Translation From Preclinical Models into Clinical Evidence," Menopause, Lippincott-Raven Publishers, United States (2014).				
WO	2009133352	A3	10/2010	Archer, F., et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study 9(1):21-31, (1992).				
WO	WO-2010146872	A1	12/2010	Ashburn, A.D., et al., "Cardiovascular , Hepatic and Renal Lesions in Mice Receiving Cortisone , Estrone and Progesterone," The Yale Journal of Biology and Medicine 35:329-340, Yale Journal of Biology and Medicine, United States (1963).				
WO	2011000210	A1	1/2011	Bartosova, L. and Bajgar, J., "Transdermal Drug Delivery in Vitro Using Diffusion Cells," Current Medicinal Chemistry 19(27):4671-4677, Bentham Science Publishers, Netherlands (2012).				
WO	2011073995	A2	6/2011	Benbow, A.L. and Waddell, B.J., "Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus During Rat Pregnancy," Biology of Reproduction 52(6):1327-1333, Society for the Study of Reproduction, United States (1995).				
WO	2011073995	A3	8/2011	Blake, E.J., et al., "Single and Multidose Pharmacokinetic Study of a Vaginal Micronized Progesterone insert (Endometrin) Compared with Vaginal Gel in Healthy Reproductive-Aged Female Subjects," Fertility and Sterility 94(4):1296-1301, Elsevier for the American Society for Reproductive Medicine, United States (2010).				
WO	2011120084	A1	10/2011	Brared Christensson, J., et al., "Positive Patch Test Reactions to Oxidized Limonene: Exposure and Relevance," Contact Dermatitis 71(5):264-272, Wiley, England (2014).				
WO	2011128336	A1	10/2011	Christen, R.D., et al., "Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin," Journal of Clinical Oncology :				
WO	2010033188	A3	11/2011					
WO	2012009778	A2	1/2012					
WO	2012024361	A1	2/2012					
WO	WO-2012055814	A1	5/2012					
WO	WO-2012055840	A1	5/2012					
WO	WO-2012065740	A1	5/2012					
WO	WO-2012098090	A1	7/2012					
WO	WO-2012116277	A1	8/2012					
WO	WO-2012118563	A2	9/2012					
WO	WO-2012120365	A1	9/2012					
WO	WO-2012127501	A2	9/2012					
WO	WO-2012156561	A1	11/2012					
WO	WO-2012156822	A1	11/2012					
WO	WO-2012158483	A2	11/2012					
WO	WO-2012166909	A1	12/2012					
WO	WO-2012170578	A1	12/2012					
WO	WO-2013011501	A1	1/2013					
WO	2012009778	A3	2/2013					
WO	WO-2013025449	A1	2/2013					
WO	WO-2013028639	A1	2/2013					

US 10,052,386 B2

Page 11

- (56) **References Cited**
- OTHER PUBLICATIONS**
- Official Journal of the American Society of Clinical Oncology 11(12):2417-2426, American Society of Clinical Oncology, United States (1993).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Differ in Allergenic Activity," Contact Dermatitis 59(6):344-352, Wiley, England (2008).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Show Specific Patch Test Reactions," Contact Dermatitis 70(5):291-299, Wiley, England (2014).
- Cicinelli, E., et al., "Direct Transport of Progesterone From Vagina to Uterus," Obstetrics and Gynecology 95(3):403-406, Lippincott Williams & Wilkins, United States (2000).
- Corbett, S.H., et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina : Focus on Vulvodynia," Southern Medical Journal 107(7):433-436, Southern Medical Association, United States (2014).
- Critchley, H.O., et al., "Estrogen Receptor Beta, but Not Estrogen Receptor Alpha, Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium," The Journal of Clinical Endocrinology and Metabolism 86(3):1370-1378, Endocrine Society, United States (2001).
- Diramio, J.A., et al., "Poly(Ethylene Glycol) Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," Masters of Science Thesis, University of Georgia, Athens, Georgia, 131 pages (2002).
- Engelhardt, H., et al., "Conceptus influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy," Biology of Reproduction 66(6):1875-1880, Society for the Study of Reproduction, United States (2002).
- Ettinger, B., et al., "Comparison of Endometrial Growth Produced by Unopposed Conjugated Estrogens or by Micronized Estradiol in Postmenopausal Women," American Journal of Obstetrics and Gynecology 176(1 Pt1):112-117, Elsevier, United States (1997).
- Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GMBH, 28 pages (2010).
- Filipsson,F., et al., "Concise International Chemical Assessment Document 5," Limonene, first draft, World Health Organization, Geneva, 36 pages (1998).
- Final Office Action dated Oct. 26, 2012 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Flyvholm, M.A. and Menne, T., "Sensitizing Risk of butylated Hydroxytoluene Based on Exposure and Effect Data," Contact Dermatitis 23(5):341-345, Wiley, England (1990).
- Franklin, R.D. and Kutteh, W.H., "Characterization of Immunoglobulins and Cytokines in Human Cervical Mucus : influence of Exogenous and Endogenous Hormones," Journal of Reproductive Immunology 42(2):93-106, Elsevier/North-Holland Biomedical Press, Ireland (1999).
- Franz, T.J., et al., "Use of Excised Human Skin to Assess the Bioequivalence of Topical Products," Skin Pharmacology and Physiology 22(5):276-286, Karger, Switzerland (2009).
- Fuchs, K.O., et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," Cutis 71(6):481-488, Frontline Medical Communications, United States (2003).
- Furness, S., et al., "Hormone therapy in Postmenopausal Women and Risk of Endometrial Hyperplasia," The Cochrane Database of Systematic Reviews 8:1-204, Wiley, England (2012).
- Gafvert, E., et al., "Free Radicals in Antigen formation: Reduction of Contact Allergic Response to Hydroperoxides by Epidermal Treatment with Antioxidants," The British Journal of Dermatology 146(4):649-656, Blackwell Scientific Publications, England (2002).
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 6 pages (2012).
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 5 pages (2012).
- Gattefosse, "Excipients for Safe and Effective Topical Delivery," <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#> (2012).
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 8 pages 2012.
- Gillet, J.Y., et al., "induction of Amenorrhea During Hormone Replacement therapy : Optimal Micronized Progesterone Dose a Multicenter Study," Maturitas 19(2):103-115, Elsevier/North Holland Biomedical Press, Ireland (1994).
- Glaser, R.L., et al., "Pilot Study : Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina," Gynecologic and Obstetric Investigation 66(2):111-118, Basel, New York, Karger., Switzerland (2008).
- Golatowski, C., et al., "Comparative Evaluation of Saliva Collection Methods for Proteome Analysis," International Journal of Clinical Chemistry 419:42-46, Elsevier, Netherlands (2013).
- Graham, J.D. and Clarke, C.L., "Physiological Action of Progesterone in Target Tissues," Endocrine Reviews 18(4):502-519, Endocrine Society, United States (1997).
- Groothuis, P.G., et al., "Estrogen and the Endometrium : Lessons Learned From Gene Expression Profiling in Rodents and Human," Human Reproduction Update 13(4):405-417, Published for the European Society of Human Reproduction and Embryology by Oxford University Press, England (2007).
- Hamid, K.A., et al., "The Effects of Common Solubilizing Agents on the intestinal Membrane Barrier Functions and Membrane Toxicity in Rats," International Journal of Pharmaceutics 379(1):100-108, Amsterdam, Elsevier/North-Holland Biomedical Press, Netherlands (2009).
- Hatton, J., et al., "Safety and Efficacy of a Lipid Emulsion Containing Medium-Chain Triglycerides," Clinical Pharmacy 9(5):366-371, American Society of Hospital Pharmacists, United States (1990).
- He, F., et al., "Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia induced by Ovariectomy Combined with Estrogen," Gynecologic and Obstetric Investigation 76(1):51-56, Karger, Switzerland (2013).
- Helmy, A., et al., "Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats," Clinical Pharmacology & Biopharmaceutics, S2, 7 pages (2014).
- Hostynk, J., et al., "Predicting absorption of fragrance chemicals through human skin," Journal of the Society of Cosmetic Chemists 46:221-229, (1995).
- Hurn, P.D. and Macrae, I.M., "Estrogen as a Neuroprotectant in Stroke," Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism 20(4):631-652, Nature Publishing Group, United States (2000).
- Hyder, S.M., et al., "Synthetic Estrogen 17Alpha-Ethynodiol induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17Beta-Estradiol," The Journal of Pharmacology and Experimental Therapeutics 290(2):740-747, American Society for Pharmacology and Experimental Therapeutics, United States (1999).
- Josh, S.G., et al., "Detection and Synthesis of a Progestagen-Dependent Protein in Human Endometrium," Journal of Reproduction and Fertility 59(2):273-285, Portland Press, England (1980).
- Kanno, J., et al., "The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses : Phase 1," Environmental Health Perspectives 109(8):785-794, N. C. National Institute of Environmental Health Sciences, United States (2001).
- Karlberg, A.T., et al., "Air Oxidation of D-Limonene (the Citrus Solvent) Creates Potent Allergens," Contact Dermatitis 26(5):332-340, Wiley, England (1992).
- Karlberg, A.T., et al., "Influence of an Anti-Oxidant on the formation of Allergenic Compounds During Auto-Oxidation of D-Limonene," The Annals of Occupational Hygiene 38(2):199-207, Oxford University Press, England (1994).
- Kaunitz, A.M. "Extended Duration Use of Menopausal Hormone therapy," Menopause 21(6):679-681, Lippincott-Raven Publishers, United States (2014).
- Kharode, Y., et al., "The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New

US 10,052,386 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention," *Endocrinology* 149(12):6084-6091, Endocrine Society, United States (2008).
- Kim, Y.W., et al., "Safety Evaluation and Risk Assessment of D-Limonene," *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 16(1):17-38, Informa Healthcare, England (2013).
- Kola, K., et al., "Enhancing Mechanism of Labrasol on intestinal Membrane Permeability of the Hydrophilic Drug Gentamicin Sulfate," *European Journal of Pharmaceutics and Biopharmaceutics : Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik E.V* 64(1):82-91, Elsevier Science, Netherlands (2006).
- Komm, B.S., et al., "Bazedoxifene Acetate : A Selective Estrogen Receptor Modulator with Improved Selectivity," *Endocrinology* 146(9):3999-4008, Endocrine Society, United States (2005).
- Kumasaka, T., et al., "Effects of Various forms of Progestin on the Endometrium of the Estrogen-Primed, Ovariectomized Rat," *Endocrine Journal* 41(2):161-169, Japan Endocrine Society, Japan (1994).
- Kuon, R.J. and Garfield, R.E., "Actions of Progestins for the inhibition of Cervical Ripening and Uterine Contractions to Prevent Preterm Birth," *Facts, Views & Vision in Obgyn* 4(2):110-119, Flemish Society of Obstetrics & Gynaecology, Belgium (2012).
- Kuon, R.J., et al., "A Novel Optical Method to Assess Cervical Changes During Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor," *American Journal of Obstetrics and Gynecology* 205(1):82.e15-82.e20, Elsevier, United States (2011).
- Kuon, R.J., et al., "Pharmacologic Actions of Progestins to inhibit Cervical Ripening and Prevent Delivery Depend on their Properties , the Route of Administration , and the Vehicle," *American Journal of Obstetrics and Gynecology* 202(5):455.e1-455.e9, Elsevier, United States (2010).
- Lanigan, R.S. and Yamarik, T.A., "Final Report on the Safety Assessment of Bht (1)," *International Journal of Toxicology* 21(2):19-94, Sage Publications, United States (2002).
- Lapez-Belmonte, J., et al., "Comparative Uterine Effects on Ovariectomized Rats After Repeated Treatment with Different Vaginal Estrogen formulations," *Maturitas* 72(4):353-358, Elsevier/ North Holland Biomedical Press, Ireland (2012).
- Lauer, A.C., et al., "Evaluation of the Hairless Rat as a Model for in Vivo Percutaneous Absorption," *Journal of Pharmaceutical Sciences* 86(1):13-18, Wiley-Liss, United States (1997).
- Leonetti, H.B., et al., "Transdermal Progesterone Cream as an Alternative Progestin in Hormone therapy," *Alternative Therapies in Health and Medicine* 11(6):36-38, InnoVision Communications, United States (2005).
- Madishetti, S.K., et al., "Development of Domperidone Bilayered Matrix Type Transdermal Patches : Physicochemical , in Vitro and Ex Vivo Characterization," *Journal of Faculty of Pharmacy* 18(3):221-229, BioMed Central, England (2010).
- Miles, R.A., et al., "Pharmacokinetics and Endometrial Tissue Levels of Progesterone After Administration by intramuscular and Vaginal Routes : A Comparative Study," *Fertility and Sterility* 62(3):485-490, Elsevier for the American Society for Reproductive Medicine, United States (1994).
- Miller, J.A., et al., "Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast," *Journal of Cancer Therapy* 3(5A), Scientific Research Publishing, United States (2012).
- Nilsson, U., et al., "Analysis of Contact Allergenic Compounds in Oxidized d-Limonene," *Chromatographia* 42:199-205, (1996).
- Non Final Office Action dated Dec. 12, 2011 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Notice of Allowance dated Sep. 11, 2013 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Opinion on Diethylene glycol monoethyl ether, Scientific Committee on Consumer Products, The SCCP adopted this opinion at its 10th plenary,27 pages (2006).
- Otterson, K. "The Drug Quality and Security Act—Mind the Gaps," *The New England Journal of Medicine* 370(2):97-99, Massachusetts Medical Society., United States (2014).
- Palamakula, A., et al., "Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components" *Pharmaceutical Technology* 74-88, (2004).
- Panay, N., et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Parasuraman, S., et al., "Blood Sample Collection in Small Laboratory Animals," *Journal of Pharmacology Pharmacotherapeutics* 1(2):87-93, Medknow Publications and Media, India (2010).
- Pfau, J.G., et al., "Selective Facilitation of Sexual Solicitation in the Female Rat by a Melanocortin Receptor Agonist," *Proceedings of The National Academy of Sciences of The United States of America* 101(27):10201-10204, National Academy of Sciences, United States (2004).
- Pickles, V.R. "Cutaneous Reactions to injection of Progesterone Solutions into the Skin," *British Medical Journal* 2(4780):373-374, British Medical Association, England (1952).
- Pinkerton, J.V. "What are the Concerns About Custom-Compounded "Bioidentical" Hormone therapy?," *Menopause* 21(12):1298-1300, Lippincott-Raven Publishers, United States (2014).
- Prausnitz, M.R. and Langer, R., "Transdermal Drug Delivery," *Nature Biotechnology* 26(11):1261-1268, Nature America Publishing, United States (2008).
- Product Safety Assessment, Diethylene Glycol Monoethyl Ether, The Dow Chemical Company Page, 5 Pages (2007).
- Provider Data Sheet, "About Dried Blood Spot Testing," ZRT Laboratory, 3 pages (2014).
- Rahn, D.D., et al., "Vaginal Estrogen for Genitourinary Syndrome of Menopause: A Systematic Review," *Obstetrics and Gynecology* 124(6):1147-1156, Lippincott Williams & Wilkins, United States (2014).
- Reisman, S.A., et al., "Topical Application of the Synthetic Triterpenoid Rta 408 Protects Mice From Radiation-induced Dermatitis," *Radiation Research* 181(5):512-520, Radiation Research Society, United States (2014).
- Ross, D., et al., "Randomized , Double-Blind , Dose-Ranging Study of the Endometrial Effects of a Vaginal Progesterone Gel in Estrogen-Treated Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 177(4):937-941, Elsevier, United States (1997).
- Ruan, X. and Mueck, A.O., "Systemic Progesterone therapy—Oral, Vaginal , injections and Even Transdermal ?," *Maturitas* 79(3):248-255, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Salem, H.F. "Sustained-Release Progesterone Nanosuspension Following intramuscular injection in Ovariectomized Rats," *International Journal of Nanomedicine* 10:943-954, DOVE Medical Press, New Zealand (2010).
- Santen, R.J. "Vaginal Administration of Estradiol : Effects of Dose , Preparation and Timing on Plasma Estradiol Levels," *The Journal of The International Menopause Society* :1-14, Informa Healthcare, England (2014).
- Schutte, S.C. and Taylor, R.N., "A Tissue-Engineered Human Endometrial Stroma That Responds to Cues for Secretory Differentiation , Decidualization , and Menstruation," *Fertility and Sterility* 97(4):997-1003, Elsevier for the American Society for Reproductive Medicine, United States (2012).
- Schweikart, K.M., et al., "Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats," *Toxicologic Pathology* 42(8):1188-1196, Sage Publications, United States (2014).
- Shao, R., et al., "Direct Effects of Metformin in the Endometrium: A Hypothetical Mechanism for the Treatment of Women with PCOS

US 10,052,386 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- and Endometrial Carcinoma," *Journal of Experimental & Clinical Cancer Research* 33:41, BioMed Central, England (2014).
- Shrier, L.A., et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *The Journal of Adolescent Health* 32(3):183-186, Elsevier, United States (2003).
- Siew, A., et al., "Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems" *Pharmaceutical Technology* 28,30-31, (2014).
- Simon, J.A. "What If the Women's Health Initiative Had Used Transdermal Estradiol and Oral Progesterone instead?," *Menopause* 21(7):769-783, Lippincott-Raven Publishers, United States (2014).
- Smyth, H.F., et al., "A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats," *Food and Cosmetics Toxicology* 2:641-642, Pergamon Press, England (1964).
- Stanczyk, F.Z., et al., "Therapeutically Equivalent Pharmacokinetic Profile Across Three Application Sites for Ag200-15 , A Novel Low-Estrogen Dose Contraceptive Patch," *Contraception* 87(6):744-749, Elsevier, United States (2013).
- Sullivan, D.W.Jr., et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology* 72:40-50, Elsevier Science Ltd, England (2014).
- Sun, J. "D-Limonene : Safety and Clinical Applications," *Alternative Medicine Review* 12(3):259-264, Alternative Medicine Review, United States (2007).
- Tang, F.Y., et al., "Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat," *Biology of Reproduction* 31(2):399-413, Society for the Study of Reproduction, United States (1984).
- Tas, M., et al., "Comparison of Antiproliferative Effects of Metformine and Progesterone on Estrogen-induced Endometrial Hyperplasia in Rats," *Gynecological Endocrinology* 29(4):311-314, Informa Healthcare, England (2013).
- Thomas, P. "Characteristics of Membrane Progestin Receptor Alpha (Mpralpha) and Progesterone Membrane Receptor Component 1 (Pgmrc1) and their Roles in Mediating Rapid Progestin Actions," *Frontiers in Neuroendocrinology* 29(2):292-312, Academic Press, United States (2008).
- Tuleu, C., et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying formulation of Progesterone Presented in a Pellet and Liquid form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences* 93(6):1495-1502, Wiley-Liss, United States (2004).
- Ueda, T., et al., "Topical and Transdermal Drug Products," *Pharmacopeial Forum* 35(3):750-764, (2009).
- Voegtlle, K.M. and Granger, D.A., "Dispatches From the interface of Salivary Bioscience and Neonatal Research," *Frontiers in Endocrinology* 5:25,Frontiers Research Foundation, Switzerland (2014).
- Waddell, B.J. and Bruce, N.W., "The Metabolic Clearance of Progesterone in the Pregnant Rat : Absence of a Physiological Role for the Lung," *Biology of Reproduction* 40(6):1188-1193, Society for the Study of Reproduction, United States (1989).
- Walter, L.M., et al., "The Role of Progesterone in Endometrial Angiogenesis in Pregnant and Ovariectomised Mice," *Reproduction* 129(6):765-777,Reproduction and Fertility by BioScientifica, England (2005).
- Wren, B.G., et al., "Effect of Sequential Transdermal Progesterone Cream on Endometrium , Bleeding Pattern , and Plasma Progesterone and Salivary Progesterone Levels in Postmenopausal Women," *The Journal of the International Menopause Society* 3(3):155-160, Informa Healthcare, England (2000).
- Wu, X., et al., "Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus," *Biology of Reproduction* 69(4):1308-1317, Society for the Study of Reproduction, United States (2003).
- Zava, D. "Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues" Script:4-5.
- Zava, D.T., et al., "Percutaneous absorption of progesterone," *Maturitas* 77:91-92, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Geelen, M.J.H., et al., "Dietary Medium-Chain Fatty Acids Raise and (n-3) Polyunsaturated Fatty Acids Lower Hepatic Triacylglycerol Synthesis in Rats," *The Journal of Nutrition* 125:2449-2456, American Institute of Nutrition, United States (1995).
- Herman, A and Herman, A.P., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," *Journal of Pharmacy and Pharmacology* 67(4):473-485, Royal Pharmaceutical Society, England (2014).
- Manson, J.E., et al., "Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials," *The Journal of the American Medical Association* 310:1353-1368, American Medical Association, United States (2013).
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 10 pages.
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Notice of Allowance, dated Dec. 15, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Feb. 11, 2015, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Notice of Allowance, dated Feb. 13, 2015, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Notice of Allowance, dated Jan. 22, 2015, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 5 pages.
- Notice of Allowance, dated Jul. 14, 2014, in U.S. Appl. No. 14/099,545, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Jul. 15, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 11 pages.
- Notice of Allowance, dated Nov. 26, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Notice of Allowance, dated Nov. 7, 2014, in U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, 14 pages.
- Office Action, dated Apr. 14, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Office Action, dated Apr. 7, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 10 pages.
- Office Action, dated Dec. 8, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 9 pages.
- Office Action, dated Feb. 18, 2015, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 8 pages.
- Office Action, dated Jul. 18, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jul. 2, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Office Action, dated Jul. 3, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 16 pages.
- Office Action, dated Jul. 30, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jun. 17, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 14 pages.
- Office Action, dated Mar. 12, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 24 pages.
- Office Action, dated Mar. 27, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Office Action, dated Oct. 2, 2014, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Office Action, dated Oct. 1, 2014, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Portman, D., et al., "One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy," *Menopause* 22(11): 7 pages, The North American Menopause Society, United States (2015).
- Rao, R. and Rao, S., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *Journal of Bioequivalence & Bioavailability* 6(4):139-143, Open Access (2014).
- Restriction Requirement, dated Mar. 28, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 7 pages.

US 10,052,386 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Restriction Requirement, dated Apr. 14, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Apr. 29, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 7 pages.
- Restriction Requirement, mailed Dec. 5, 2014, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 9 pages.
- Restriction Requirement, dated Jul. 3, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 6 pages.
- Restriction Requirement, dated Mar. 16, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Mar. 20, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Mar. 26, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 7 pages.
- Restriction Requirement, dated May 13, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Nov. 4, 2014, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 7 pages.
- Schindler, A.E., et al., "Classification and pharmacology of progestins," *Maturitas* 46S1:S7-S16, Elsevier Ireland Ltd., Ireland (2003).
- Sitruk-Ware, R., "Pharmacological profile of progestins," *Maturitas* 47:277-283, Elsevier Ireland Ltd., Ireland (2004).
- Stanczyk, F.Z., "All progestins are not created equal," *Science* 68:879-890, Elsevier Inc., United States (2003).
- Stanczyk, F.Z., et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause* 12(2):232-237, The North American Menopause Society, United States (2005).
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective," *Climacteric* 17(Suppl 2):8-11, International Menopause Society, United Kingdom (2014).
- Stephenson, K., "Transdermal Progesterone: Effects on Menopausal Symptoms and on Thrombotic, Anticoagulant, and Inflammatory Factors in Postmenopausal Women," *International Journal of Pharmaceutical Compounding* 12(4):295-304, IJPC, United States (2008).
- Weintraub, A., "Women Fooled by Untested Hormones From Compounding Pharmacies," *Forbes*, accessed at <http://onforbs.es/1LIUm1V>, accessed on Feb. 23, 2015, 3 pages.
- Co-pending U.S. Appl. No. 14/671,655, Inventors Amadio, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- Co-pending U.S. Appl. No. 14/671,651, Inventors Cacase, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- Acarturk, Fusun, Mucoadhesive Vaginal Drug Delivery Systems, Recent Patents on Drug Delivery & Formulation, vol. 3, pp. 193-205, 2009, Bentham Science Publishers, Ltd.
- Bhavnani, Bhagu R., et al., Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy, *J Clin Endocrinol Metab.*, vol. 97(3), Mar. 2012, The Endocrine Society 2011.
- Bhavnani, Bhagu R., et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ER) and ERA and ERB, *Endocrinology*, Oct. 2008, vol. 149(10), pp. 4857-4870, The Endocrine Society 2008.
- Du, Joanna Y., et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, vol. 20(11), pp. 000-000, The North American Menopause Society 2013.
- Fotherby, K., Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, *Contraception*, vol. 54, pp. 59-69, Elsevier Science, Inc. 1996.
- Fuchs, Katie O., et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Pharmacology/Cosmetology*, vol. 5(1), 2006.
- Hargrove, Joel T., et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, *Estrogen Replacement Therapy, Obstetrics & Gynecology*, vol. 73(4), pp. 606-612, Apr. 1989, The American College of Obstetricians and Gynecologists.
- ISR and written opinion for PCT/US/13/46442, dated Nov. 1, 2013.
- ISR and written opinion for PCT/US/13/46443, dated Oct. 31, 2013.
- ISR and written opinion for PCT/US/13/46444, dated Oct. 31, 2013.
- ISR and written opinion for PCT/US/13/46445, dated Nov. 1, 2013.
- Kincl, Fred A., et al., Short Communication, Increasing Oral Bioavailability of Progesterone by Formulation, *Journal of Steroid Biochemistry*, vol. 9, pp. 83-84 Pergamon Press 1978, Great Britain.
- The Journal of the North American Menopause Society (NAMS), Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society, *Menopause*, vol. 20(9), pp. 888-902, The North American Menopause Society 2013.
- Panay, Nick, The 2013 British Menopause Society & women's Health Concern recommendations on hormone replacement therapy, *Menopause International, The Integrated Journal of Postreproductive Health*, vol. 0(0), Sage 2013.
- Patel, Dipen, et al., Transdermal Drug Delivery System: A Review, *The Pharma Innovation, The Pharma Journal*, vol. 1(4), 2012.
- Sarrel, Philip M., et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, *American Journal of Public Health, Research and Practice*, pp. e1-e6, Published online ahead of print Jul. 18, 2013.
- Shufelt, Chrisandra L., et al., Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, *Menopause: The Journal of the North American Menopause Society (NAMS)*, vol. 21(3), pp. 000-000, The North American Menopause Society 2013.
- Simon, James, et al., Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet, *Obstetrics & Gynecology*, vol. 112(5), pp. 1053-1060, pp. 373-402, Nov. 2008.
- Sitruk-Ware, Regine, et al., Oral Micronized Progesterone, *Contraception*, vol. 36(4), Oct. 1987.
- Sitruk-Ware, Regine, Progesterones in hormonal replacement therapy: new molecules, risks, and benefits, *Menopause: The Journal of the North American Menopause Society (NAMS)*, vol. 9(1), pp. 6-15, The North American Menopause Society 2002.
- Smith, Nicholas L., et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, *JAMA Intern Med*, pp. e1-e7, published online Sep. 30, 2013.
- Stanczyk, Frank, et al., Ethinyl estradiol and 17B-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, *Contraception*, vol. 87, pp. 706-727, Elsevier 2013.
- USPTO, Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.
- USPTO, Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.
- USPTO, Notice of allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.
- USPTO, Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO, Restriction/Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO, Restriction/Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- Whitehead, M. I., et al., Absorption and Metabolism of Oral Progesterone, *The British Medical Journal*, vol. 280(6217), pp. 825-827, Mar. 22, 1980, BMJ Publishing Group, JSTOR.
- Wood, Charles E., et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, *Breast Cancer Res Treat*,

US 10,052,386 B2

Page 15

(56)

References Cited

OTHER PUBLICATIONS

- vol. 101, pp. 125-134, published online Jul. 14, 2006, Springer Science + Business Media B.V. 2006.
- Acog, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician—Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, *Obstetrics & Gynecology*.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaya, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brandstatter-Kuhnert, M. Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, Acta, vol. 6, pp. 847-853, 1959, Univ. Innsbruck.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moléculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiolophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moléculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moléculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Física, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helveticae, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, Pharmaceutical Research, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, Journal of General Internal Medicine, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochimica Acta, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.

US 10,052,386 B2

Page 16

(56)

References Cited

OTHER PUBLICATIONS

- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helveticae, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PhamSciTech, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. SteroidBiochem. Mol. Biol. (2013), Elsevier.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II. vol. 1 pp. 127-139, 1968, Mikrochimica Acta.
- Kuhnert-Brandstaetter, M & Lnder, R, Zur Hydratbildung bei Steroidhormonen, Sci. Pharm., vol. 41(2) pp. 109-116, 1973.
- Kuhnert-Brandstatter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, Microchemical Journal 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, Journal of Steroid Biochemistry & Molecular Biology, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , Jour. of Pharm. Sci., vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, Pharmaceutical Research, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, Fertility and Sterility, vol. 79(1), Jan. 2003.
- Lewis, John G, et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , Maturitas, The European Menopause Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , Steroids, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, J Thermal Anal., vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , Journal of Animal Science, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, Chemistry and Industry, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, J. Steroid Biochem. Mol.Biol. (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone, J. Pharmaceutical Sciences, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , Drug Devel. & Indust. Pharmacy,35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , Clinical Endocrinology, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alan/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, Arch Pharm Res, vol. 31(1), pp. 111-116, 2008.

US 10,052,386 B2

Page 17

(56)

References Cited

OTHER PUBLICATIONS

- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , European Journal of Pharmaceutics and Biopharmaceutics, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, Crystal Structure Comm., Int'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, Intl. Jour. of Pharma., vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, Adv. Drug Delivery Reviews, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%_20atches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, Pharmaceutical Research, vol. 15(5) pp. 794-99,1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , J Steroids Horm Sci, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, Asian J. Chem., vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), J. Steroid Biochem.Mol. Biol. (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, Natioinal Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaldrich.com/catalog/product/sigma/p7556>.
- Acarturk, "Mucoadhesive Vaginal Drug Delivery System," Recent Patents on Drug Delivery & Formulation, 3(3):193-205, 2009.
- Fuchs et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," Aesthetic Dermatology, 8(1):14-19, 2006.
- Panay et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," DOI: 0.1177/1754045313489645, min.sagepub.com. Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
- Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547. 2009. Abstract Only.
- Azure Pharma, Inc., "ELESTRINTM—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, 2009.
- Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, 2005.
- Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882, 2012.
- Diramio, "Polyethylene Glycol Methacrylate/Dimethylacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia—Masters of Science Thesis, 131 pages, 2004. http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1.
- Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171, 1997. Abstract Only.
- Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345, 2000. Abstract Only.
- Knuth et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167, 1993. Abstract Only.
- Lucy et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle," Biol Reprod., 35(2):300-11, 1986. Abstract Only.
- NuGen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, 3 pages, undated.
- NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, 4 pages, undated.
- Panchagnula et al., "Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies," J Pharm Pharmacol.,43(9):609-14, 1991. Abstract Only.
- Salole, "The physiochemical properties of oestradiol," Journal of Pharmaceutical & Biomedical Analysis, 5(7):635-648, 1987.
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," Pharmaceutical Research, 21(2):201-230. 2004.
- Tahition Noni, "Body Balance Cream," http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/, 1 page, undated.
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," Skin Pharmacol Physiol., 19:106-121, 2006. http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf.
- International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.
- International Search report for corresponding International Application No. PCT/US12/66406, dated Jan. 24, 2013.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, Fountain Journal of Nat. and Appl. Sciences, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, [http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index\[Feb. 3, 2014 1:37:50 PM\]](http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index[Feb. 3, 2014 1:37:50 PM]).

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(56)

References Cited

OTHER PUBLICATIONS

- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, Sci. Agric., vol. 62(3), pp. 291-295, 2005, Piracicaba, Brazil.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, Clean Techn Environ Policy, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, Obstetrics & Gynecology, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate—Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, Cereal Chem., vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- International Search Report and Written Opinion of International Application No. PCT/US2015/023041, Korean Intellectual Property Office, Republic of Korea, dated Jun. 30, 2015, 14 pages.
- Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences* 11(3):42-49, Niper, India (Jul.-Sep. 2010).
- Abdalla, A., et al., "A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets," *Eur J Pharm Sci* 35(5):457-464, Elsevier, Netherlands (2008).
- Falconer, J.R., et al., "The Effects of Supercritical Carbon Dioxide Processing on Progesterone Dispersion Systems: A Multivariate Study," *AAPS Pharm. Sci. Tech.* 13(4): 1255-1265, Springer, USA (2012).
- Restriction Requirement, dated Feb. 6, 2013, in U.S. Appl. No. 13/684,002, Bernick, B.A., filed Nov. 21, 2012, 9 pages.
- Office Action, dated Oct. 7, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 12 pages.
- Office Action, dated Jul. 15, 2016, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 15 pages.
- Office Action, dated Apr. 21, 2017, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 13 pages.
- Office Action, dated Jul. 2, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 9 pages.
- Notice of Allowance, dated Feb. 10, 2016, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 10 pages.
- Office Action, dated Oct. 26, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 10 pages.
- Office Action, dated Nov. 7, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.
- Office Action, dated Mar. 30, 2016, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 13 pages.
- Office Action, dated Jun. 19, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 11 pages.
- Office Action, dated Mar. 23, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.
- Notice of Allowance, dated Sep. 29, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Notice of Allowance, dated Aug. 4, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 11 pages.
- Notice of Allowance, dated Jun. 15, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Office Action, dated Jul. 20, 2016, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 12 pages.
- Office Action, dated Jun. 16, 2017, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 13 pages.
- Office Action, dated Oct. 8, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 7 pages.
- Notice of Allowance, dated Feb. 1, 2016, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 6 pages.
- Office Action, dated Sep. 28, 2017, in U.S. Appl. No. 15/454,898, Bernick, B.A., filed Mar. 9, 2017, 10 pages.

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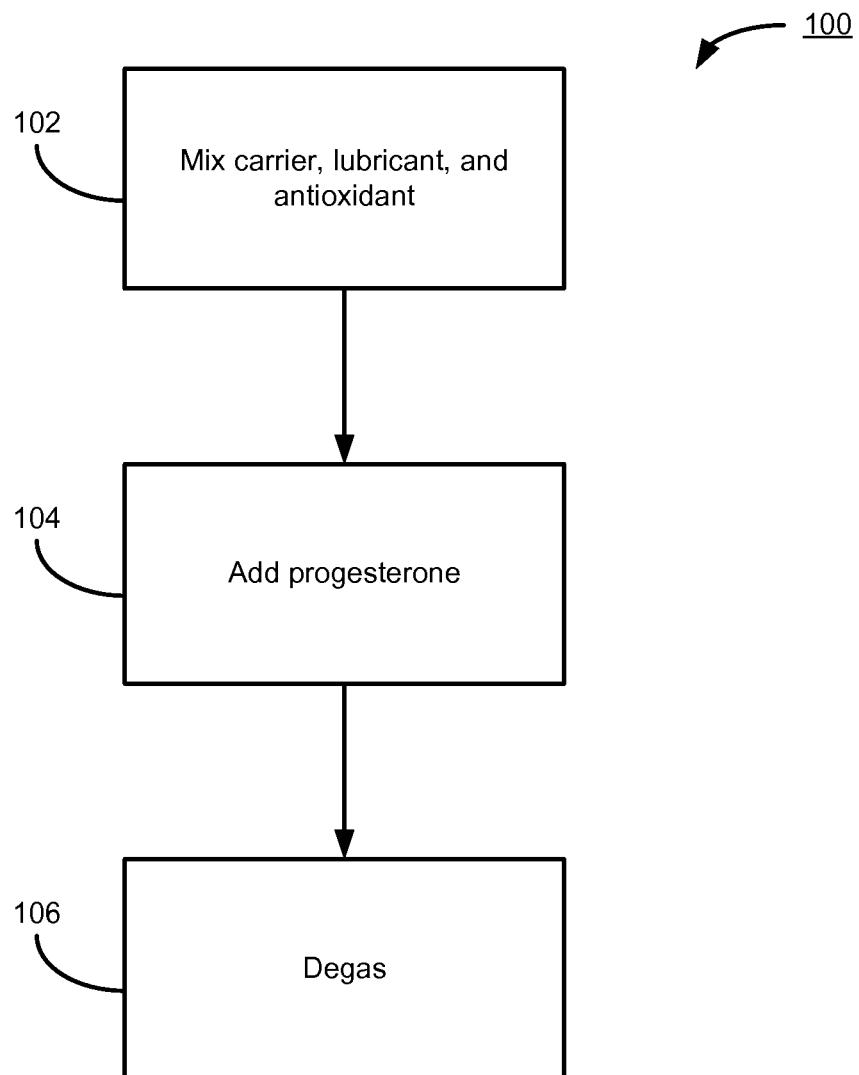


FIG. 1

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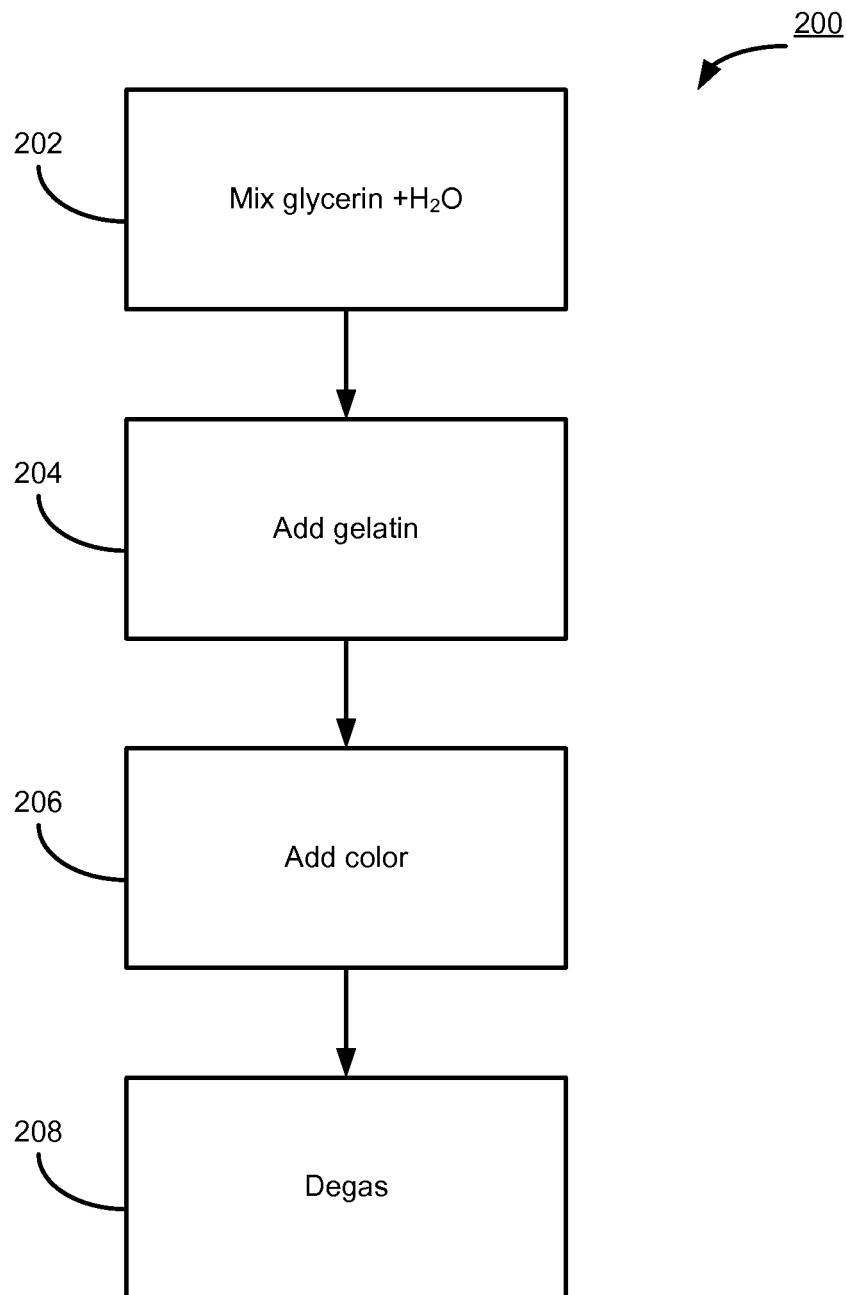


FIG. 2

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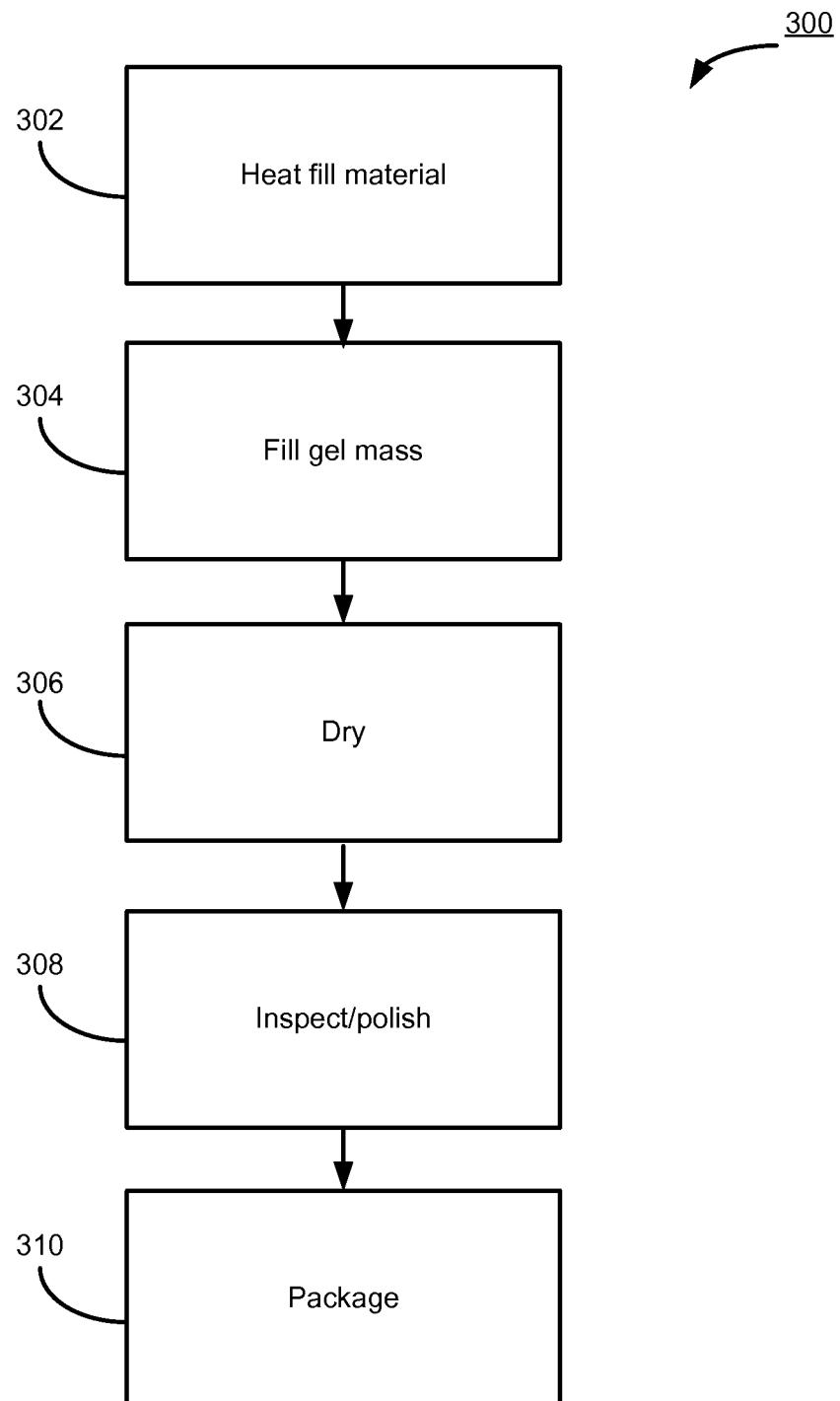


FIG. 3

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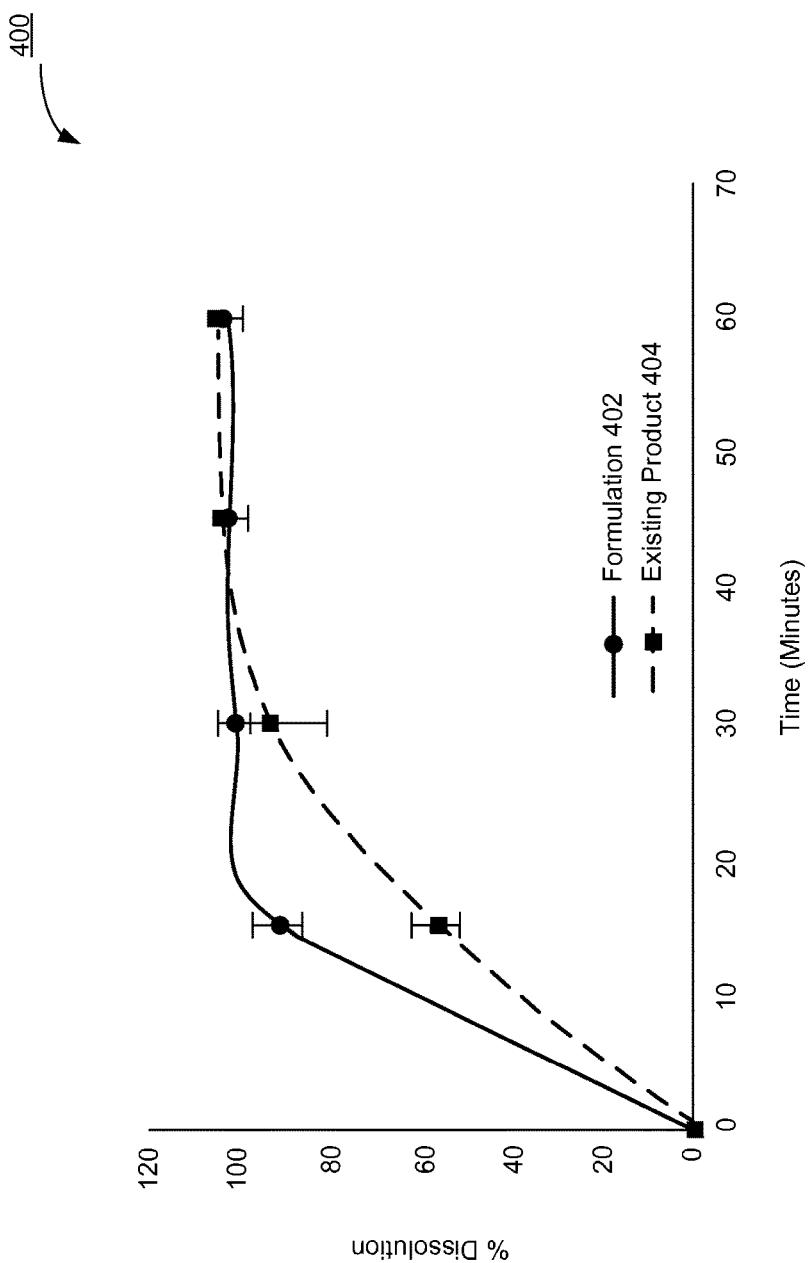


FIG. 4

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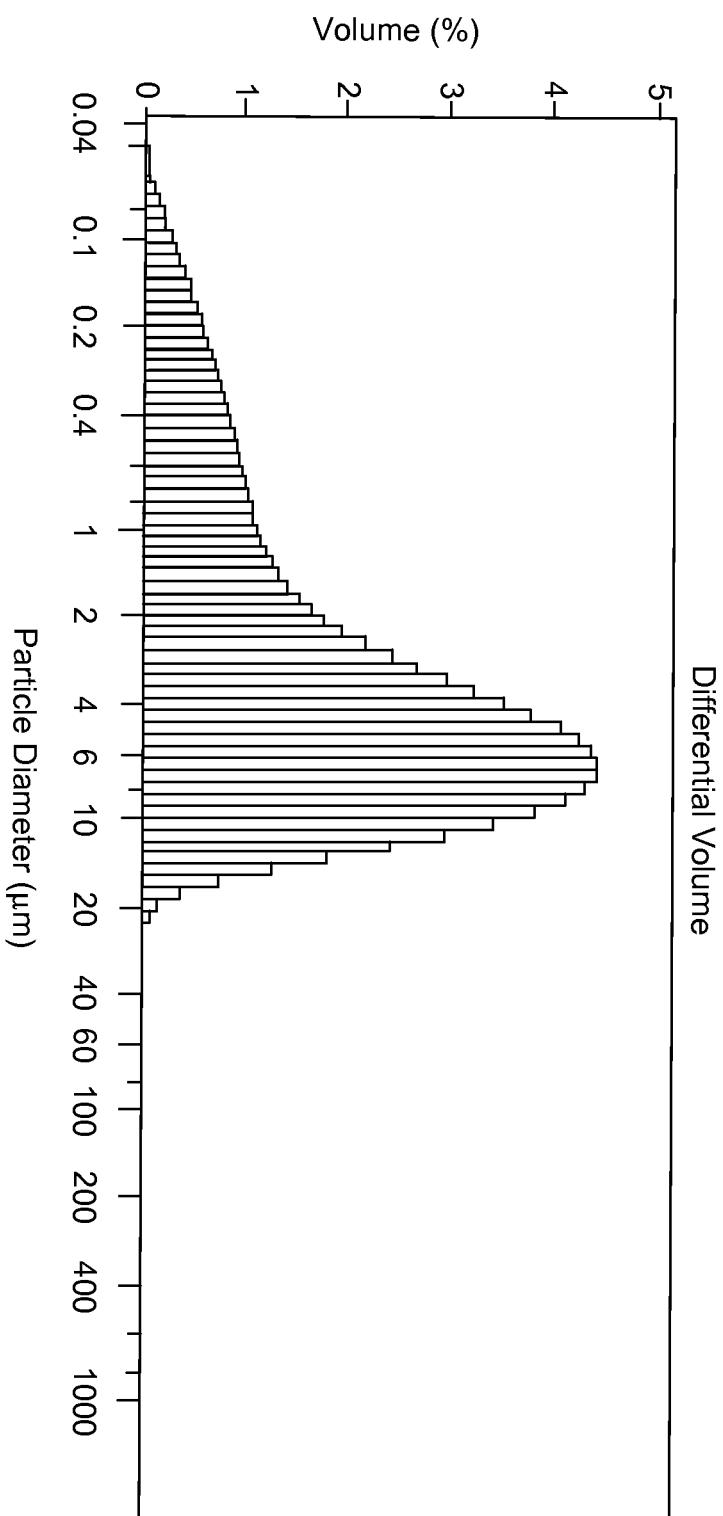


FIG. 5

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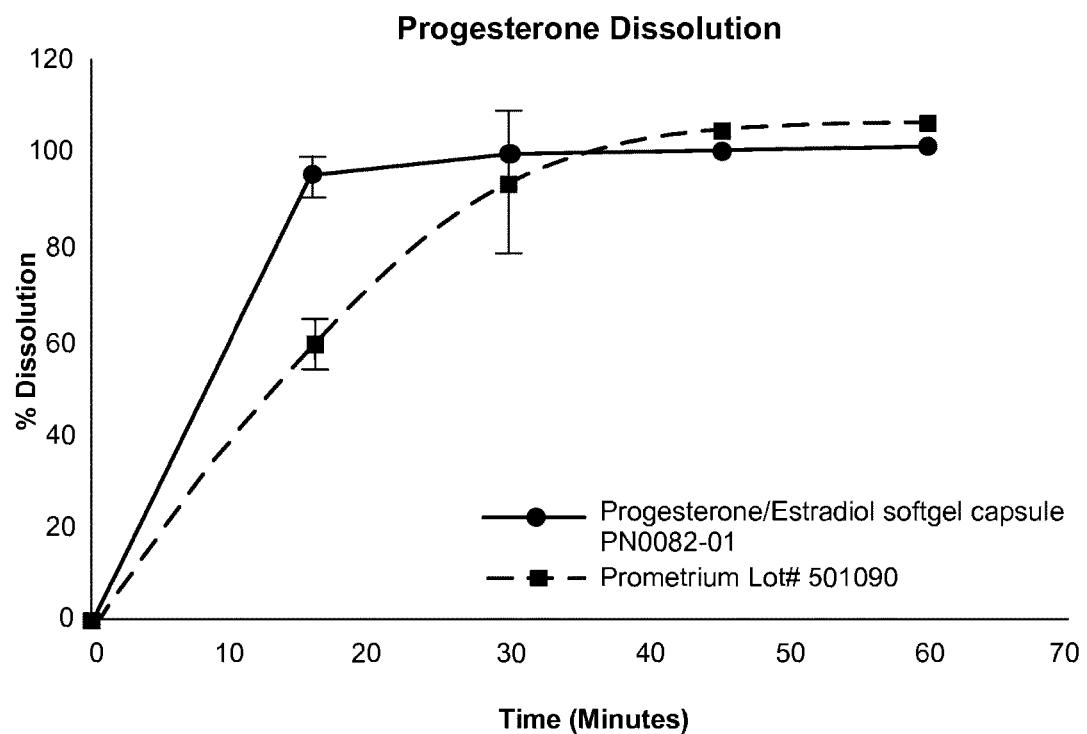


FIG. 6

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1**PROGESTERONE FORMULATIONS****CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a National Stage application under 35 U.S.C. § 371 of International Application Ser. No. PCT/US2013/046442, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 18, 2013, and claims priority to the following U.S. Patent Applications: U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012; U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Nov. 21, 2012; U.S. Patent Application Ser. No. PCT/US2013/023309, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Jan. 25, 2013; U.S. patent application Ser. No. 13/843,362, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Mar. 15, 2013; and U.S. patent application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF INVENTION

The disclosure relates to progesterone formulations. Various progesterone formulations may be used in hormone therapies for menopausal, peri-menopausal and post-menopausal females, for example, to mitigate side effects from estrogen replacement therapy. In addition, various progesterone formulations may be used to prevent preterm delivery in pregnant women having a shortened cervix.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to supplement hormone levels in women who lack adequate hormone production. It can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones.

HRT is available in various forms. One therapy involves administration of low dosages of one or more estrogen(s) or one or more chemical analogues. Another involves administration of progesterone or one or more chemical analogues. Among other effects, progesterone administration acts to mitigate certain undesirable side effects from estradiol administration or naturally-occurring elevated blood levels including endometrial hyperplasia (thickening) and prevention or inhibition of endometrial cancer. Progesterone is a C-21 steroid sex hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone is hydrophobic, having a reported aqueous solubility of 0.007 ± 0.0 mg/ml. Progesterone is poorly absorbed when administered orally.

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Conventional progesterone therapeutics include the administration of PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug, formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction.

The active ingredient is considered to be structurally identical to naturally occurring progesterone produced by a woman's body (also known as a "bioidentical").

Clinical trials involving PROMETRIUM have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean pharmacokinetic parameters listed in Table 1 (see Table 1, package insert for PROMETRIUM).

TABLE 1

Pharmacokinetic Parameters of PROMETRIUM Capsules			
Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 \pm 21.9	38.1 \pm 37.8	60.6 \pm 72.5
T_{max} (hr)	1.5 \pm 0.8	2.3 \pm 1.4	1.7 \pm 0.6
AUC (0-10)(ng·hr/ml)	43.3 \pm 30.8	101.2 \pm 66.0	175.7 \pm 170.3

The unusually high variability in the C_{max} and AUC, as evidenced by the large reported standard deviation, indicates that a significant percentage of patients are overdosed or receive a sub-optimal dose.

The presence of peanut oil in the formulation excludes patients who are allergic to peanut oil. Peanut oil, like other peanut products, may act as an allergen. Indeed, there is a portion of the population that has severe reactions to peanut oil. Peanut allergies are becoming a significant health concern. Food allergies are a leading cause of anaphylaxis, with approximately 200 deaths occurring annually in the United States. While incidence and prevalence are not entirely known, it is suspected that about 6% of children and 4% of adults in North America are affected by food allergies. Many food allergies experienced by children are generally outgrown in adulthood with the exception of peanut allergies.

Progesterone and its analogues can be used to treat a variety of medical conditions, including acute diseases or disorders, as well as chronic diseases and disorders associated with long-term declines of natural progesterone levels.

Accordingly, improved formulations of progesterone would be advantageous.

SUMMARY OF THE INVENTION

Various pharmaceutical formulations are disclosed herein. For example, pharmaceutical formulations are disclosed comprising ultra-micronized progesterone. Moreover, pharmaceutical formulations are disclosed comprising formulations of ultra-micronized progesterone, wherein the ultra-micronized progesterone is combined with a suitable excipient.

Thus, in various illustrative embodiments, the invention comprises an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form, in solubilized form, or in micronized and partially soluble form in a carrier that comprises a medium chain fatty

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acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester. In some such embodiments the progesterone is ultra-micronized. In some such embodiments, at least about 80 wt % of the total progesterone is micronized. The fatty acids can be predominantly (>50 wt %): C6 to C12 fatty acids, C6 to C10 fatty acids, C8 to C12 fatty acids, or C8 to C10 fatty acids, the esters can be mono-, di-, or triesters or mixtures thereof, and the glycols can be glycerol, polyethylene glycol or propylene glycol or mixtures thereof. Some embodiments comprise a non-ionic surfactant that comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate embodiments of the disclosure, and together with the description serve to explain the principles of the disclosure.

FIG. 1 illustrates a process to produce fill material in accordance with various embodiments;

FIG. 2 illustrates a process to produce softgel capsules in accordance with various embodiments;

FIG. 3 illustrates a process to produce softgel capsules in accordance with various embodiments; and

FIG. 4 illustrates a dissolution study of a formulation in accordance with various embodiments.

FIG. 5 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 6 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

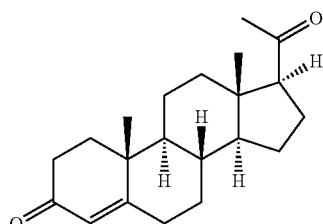
According to various embodiments, a pharmaceutical formulation comprising ultra-micronized progesterone is provided. As described in detail here, various carriers, lubricants, and other excipients may be included. In further embodiments, ultra-micronized progesterone formulations provide improved bioavailability and other pharmacokinetic improvements.

Definitions

Unless otherwise specified, the following definitions apply.

The term “ultra-micronized progesterone,” as used herein, includes micronized progesterone having an X50 value below about 20 microns and/or having an X90 value below about 25 microns.

A chemical structure of progesterone is depicted below:



The term “administer,” “administration,” “deliver” or “delivery” (collectively “administration”), as used herein,

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means administration to the body via, without limitation, tablets, capsules, softgel capsules, injections, transdermal patches, creams, gels, vaginal suppositories including gelcaps or other mechanisms known in the art or hereinafter developed. The term “administration” may also mean direct application of softgel contents into the vagina, such as by accessing the softgel contents opening or rupturing the softgel capsule to liberate the contents therein.

The term “X50,” as used herein, means that half of the particles in a sample are smaller in diameter than a given number. For example, ultra-micronized progesterone having an X50 of 5 microns means that, for a given sample of ultra-micronized progesterone, half of the particles have a diameter of less than 5 microns. In that regard, similar terms, in the form XYY mean that YY percent of the particles in the sample are smaller in diameter than a given number. For example, X90 means that ninety percent of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-contain substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances. For further illustration, C6-C14 fatty acids, C6-C12 fatty acids, and C8-C10 fatty acids are all medium chain fatty acids and may be used in instances in which this specification calls for use of medium chain fatty acids, e.g., medium chain fatty acid esters of glycerol or other glycols.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in gastric juices compared to PROMETRIUM.

The term “gastric juices” means the watery, acidic digestive fluid that is secreted by various glands in the mucous membrane of the stomach and consists chiefly of hydrochloric acid, pepsin, rennin, and mucus.

The term, “API,” as used herein, refers to active pharmaceutical ingredient. In formulations, the API is progesterone.

The term “excipients,” as used herein, refers to non-API substances such as carriers, solvents, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “carrier,” as used herein, means any substance or mixture of substances that may be mixed with or contain an API (e.g., ultra-micronized progesterone).

The term “capsule,” as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products, and includes hard or soft shell capsules.

The term “softgel,” includes soft shell capsules, including soft-gelatin capsules and soft vegetable-based capsules, and soft capsules made from other materials providing the composition of such soft capsules are compatible with the formulations of the various embodiments described herein. A softgel may comprise two primary phases: a gel or vegetable-based capsule and a fill material of the pharmaceutical formulation as described herein.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} and optionally T_{max} .

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The terms "pharmacokinetics" and "pharmacokinetic measurements" include assessments and determinations to study absorption, distribution, metabolism, and excretion of a drug.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone blood concentration to reach the maximum value.

Optionally, the term, " $T_{1/2}$ " as used herein, refers to the time that it takes for progesterone blood concentration to decline to one-half of the maximum level.

Collectively AUC, C_{max} , and optionally T_{max} and $T_{1/2}$, are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

DESCRIPTION

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone, and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %, based on the weight of the entire fill, i.e., the liquid pharmaceutical formulation.

Other embodiments disclosed herein further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, when compared to equal dosages of PROMETRIUM. Blood level variability is also compared at equal sampling times following administration.

According to the PROMETRIUM prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T_{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC ₀₋₁₀ (ngxhr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

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In particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure include the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States") in a subject in need of treatment, and with a non-toxic effective amount of said formulations.

As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. Particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 nm. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The

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Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

In various embodiments, ultra-micronized progesterone has an X50 value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns; and an X90 value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

In various embodiments, ultra-micronized progesterone is formulated with peanut and peanut-oil free excipients.

In various embodiments, the carrier is selected to enhance dissolution and suspension properties of progesterone. In further various embodiments, the carrier is selected to enhance absorption of the API by cells of a mammal. For example, certain carriers may be selected to enhance absorption of the other formulation components, including the API. Absorption may comprise absorption into any cell and particularly absorption into digestive system cells, such as intestinal cells, and cells of the female reproductive system, such as the vagina and the cervix. Selected mono/di/triglycerides are particularly suited to aid in cellular absorption

In various embodiments, the carrier may comprise medium chain fatty acids. Suitable carriers include caproic fatty acid; caprylic fatty acid; capric fatty acid; lauric acid; myristic acid; linoleic acid; succinic acid; glycerin; propylene glycol; caprylic/capric triglycerides; caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; caprylic/capric/succinic triglycerides; polyethylene glycol; propylene glycol dicaprylate/dicaprate; and combinations and derivatives thereof.

Suitable carriers further include esters of saturated coconut and palm kernel oil and derivatives thereof, including fractionated coconut oils and palm kernel oils thereof; and triglycerides of fractionated vegetable fatty acids, and derivatives thereof and combinations thereof. In further various embodiments, the carrier may comprise one or more monoglycerides, diglycerides, triglycerides, and combinations thereof such a suitable carrier is available commercially under the trademark MIGLYOL (caprylic/capric triglyceride) (Sasol Germany, GmbH). MIGLYOL products comprise esters of saturated coconut and palm kernel oil-derived caprylic and capric fatty acids, glycerin and/or propylene glycol. Suitable MIGLYOL products include MIGLYOL 810 (Caprylic/Capric Triglyceride) MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 818 (Caprylic/Capric/Linoleic Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride).

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Additional examples include a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the CAPMUL brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol:Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof. In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL; TRANSCUTOL, MIGLYOL and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM and a non-ionic surfactant; and CAPMUL MCM and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for suspension and/or solubilization of progesterone. CAPMUL MCM and a non-ionic surfactant, e.g., GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, CAPMUL MCM and GELUCIRE were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be, e.g., 8:1 or greater, e.g., 60 to 70:1.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments, oils used to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, progesterone is soluble in the oils at room temperature, although it may be desirable to warm certain oils initially during manufacture to improve viscosity. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 50° C. In illustrative embodiments, GELUCIRE 44/14 is heated to about 65° C. and CAPMUL MCM is heated to about 40° C. to facilitate mixing of the oil and non-ionic surfactant, although such heating is not necessary to dissolve the estradiol or progesterone.

In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8

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wt % or higher, or 1.0 wt % or higher. Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, CAPMUL MCM, CAPMUL MCM C10 (Glyceryl Monocaprate), CAPMUL MCM C8 (Glyceryl Monocaprylate), and CAPMUL MCM C8 EP (Glyceryl Monocaprylate). These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, MIGLYOL 810 and MIGLYOL 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, CAPMUL PG-8, CAPMUL PG-2L EP/NF (Propylene Glycol Dilaurate), CAPMUL PG-8 NF (Propylene Glycol Monocaprylate), CAPMUL PG-12 EP/NF (Propylene Glycol Monolaurate) and CAPRYOL (Propylene glycol monocaprylate (type II) NF). Other illustrative examples include MIGLYOL 840 (Propylene Glycol Dicaprylate/Dicaprante).

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, GELUCIRE 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of GELUCIRE, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids.

It will be understood that commercially available fatty acid esters of glycerol and other glycols are often prepared from natural oils and therefore may comprise components additional to the fatty acid esters that comprise the predominant (by weight) component(s) and that therefore are used to characterize the product. Such other components may be, e.g., other fatty acid triglycerides, mono- and diesters, free glycerol, or free fatty acids. So, for example, when an oil/solubilizing agent is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for CAPMUL MCM C8 describes CAPMUL MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

By way of further example, MIGLYOL 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

Specifically, a product information sheet for MIGLYOL by SASOL provides the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic (C14:0) acid	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

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Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in C8-C10 triglycerides, and a thickening agent, it will be understood that the fatty acid esters component of the formulation may be, e.g., MIGLYOL 812 or a similar product.

By way of further illustration, GELUCIRE 44/14 is generally described as lauroyl polyoxyl-32 glycerides, i.e., polyoxyethylene 32 lauric glycerides (which is a mixture of mono-, di-, and triesters of glycerol and mono- and diesters of PEGs) because the fatty acid composition is 30 to 50% lauric acid and smaller amounts of other fatty acids, e.g., up to 15% caprylic acid, up to 12% capric acid, up to 25% myristic acid, up to 25% palmitic acid, and up to 35% stearic acid. The product may also contain small amounts of non-esterified glycols. Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising C8 to C18 fatty acid esters of glycerol and polyethylene glycol, it will be understood that the thickening agent component of the formulation may be, e.g., GELUCIRE 44/14 or a similar product.

Similarly, where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, it will be understood that the thickening agent component of the formulation may be, e.g., TEFOSE 63 (PEG-6 palmitostearate and ethylene glycol palmitostearate) or a similar product.

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL MCM) and polyethylene glycol glycerides (e.g., GELUCIRE) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 °C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The progesterone can be added as the mixture cools, e.g., to below about 40 °C or to below about 30 °C, even down to room temperature.

In certain embodiments, an anionic and/or a non-ionic surfactant is used. Exemplary non-ionic surfactants may include one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE, including, for example, GELUCIRE 44/11 and GELUCIRE 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, GELUCIRE 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, Tables below. Other non-ionic surfactants include, e.g., LABRASOL (Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF PEG-8 Caprylic/Capric Glycerides (USA FDA IIG)(Gattefosse) and LABARAFIL (corn/apricot oil PEG-6 esters) (Gattefosse).

In various embodiments, a lubricant is used. Any suitable lubricant may be used, such as, for example and without limitation, lecithin, and in various embodiments, a mixture of polyethylene glycol ("PEG") esters, glycerides, and PEG, such as is commercially available under the trade name GELUCIRE (Gattefosse, FR) may also be used as a lubricant. Suitable lubricants may also comprise calcium stearate,

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ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, poloxamer, glycols, and phospholipid mixtures. In particular, a mixture of polyethylene glycol esters, glycerides, and PEG such as GELUCIRE 44/14, may be used as a lubricant. GELUCIRE 44/14 is a non-ionic water dispersible surfactant, also known as lauroyl macrogol-32 glycerides EP and lauroyl polyoxyl-32 glycerides NF. In various embodiments, GELUCIRE 44/14 acts as a suspension agent.

In various embodiments, an antioxidant is used. Any suitable antioxidant may be used, such as, for example and without limitation, butylated hydroxytoluene. Butylated hydroxytoluene, a derivative of phenol, is lipophilic and is thus suited to being intermixed with ultra-micronized progesterone and carriers disclosed or contemplated herein.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises progesterone, at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of one or more glycols, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized.

Pharmaceutical formulations in accordance with various embodiments comprise ultra-micronized progesterone. In further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, and a lubricant. In still further embodiments a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, a lubricant, and optionally an antioxidant. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and a medium chain triglyceride as a carrier. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and monoglycerides/diglycerides/triglycerides of caprylic/capric acid as a carrier. Various further embodiments also comprise lecithin and optionally butylated hydroxytoluene.

In additional embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone and at least one

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carrier, a lubricant, optionally an antioxidant, and other pharmaceutically acceptable excipients. For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Formulations in accordance with various embodiments may be administered alone or combination with one or more other drugs (or as any combination thereof). For example, formulations in accordance with various embodiments may also comprise estradiol.

In various embodiments, ultra-micronized progesterone is administered in a capsule. Capsules may be prepared using one or more film forming polymers. Suitable film forming polymers include natural polymers, such as gelatin, and synthetic film forming polymers, such as modified celluloses. Suitable modified celluloses include, but are not limited to, hydroxypropyl methyl cellulose, methyl cellulose.

Hard or soft shell capsules can be used to administer the API. In certain embodiments, capsules may be prepared by forming the two capsule halves, filling one of the halves with the fill solution, and then sealing the capsule halves together to form the finished capsule.

Hard shell capsules may be prepared by combining the "Body" and the "Cap". The "Body" of the capsule is filled with the "fill mass" and then closed with the "Cap". The "Body"/"Cap" interface is then sealed/banded.

Soft gelatin capsules may be prepared using a rotary die encapsulation process, as further described below.

Suitable shell additives, for either a hard or soft shell capsules, may include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids, and combinations thereof. The main ingredients of the capsule shell is primarily gelatin (or a gelatin substitute for non-gelatin capsules), plasticizer, and purified water. Hard shell and soft shell capsules differ primarily in the amount of plasticizer present that is used in the capsule shell.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include, but are not limited to, glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light-sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to minimize cross-linking of the gelatin.

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In accordance with various embodiments, a softgel dosage form is used.

A softgel comprises two primary phases: a gel capsule and a fill material. The softgel may comprise a gelatin material in a relatively solid or stiff form. The softgel may define an inner volume that may contain the fill material. Dissolution of the softgel may commence at various points, such as along the digestive tract (mouth, esophagus, stomach and intestines), or other body cavities, such as the vaginal cavity.

As the softgel dissolves, the inner volume may come into fluid communication with the digestive system, allowing the fill material to leach outside the softgel. A softgel may also be punctured, cut, or otherwise opened outside a body. The fill material may then be poured or squeezed outside the gel capsule and applied on or in the body, such as within the vaginal cavity.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl esters (collectively known as "parabens") or combinations thereof.

The fill material may comprise a liquid, such as an oil, a solution, a suspension, or other acceptable forms. The active ingredient or active ingredient may be contained within the liquid.

Formulations in accordance with various embodiments may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Ultra-micronized progesterone in accordance with various embodiments may be formulated as a vaginal suppository or vaginal cream for administration onto the vulva or into the vagina, cervix, or uterus of a human. Capsules (e.g., softgels) containing ultra-micronized progesterone also may be administered vaginally, including insertion of a capsule directly into the vaginal cavity or delivery of such capsule contents into the vaginal cavity. Ultra-micronized progesterone, in accordance with various embodiments, may be formulated for intraperitoneal administration, and atomization, such as with nasal mist administration.

In accordance with various embodiments, enhanced bioavailability of progesterone is provided, such as over conventional progesterone formulations wherein it is well known that commercially available formulations of progesterone are poorly or inconsistently absorbed. While not bound by theory, the elements of the present formulation provide the enhanced performance characteristics as further described herein, including, for example and without limitation, improved bioavailability and the potential to be able to reduce the administered dosage strength compared to presently available progesterone formulations. Bioavailability comparisons to commercially available forms, such as tablet forms, may be determined by standard pharmacokinetic techniques.

In accordance with various embodiments, food effects are reduced, e.g., relative to comparative progesterone products.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

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Capsules may be arranged in blisters or cartridges or bottles.

According to various embodiments, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having delivery days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no API or hormone (e.g., progesterone) may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each dose (e.g., each softgel) may contain ultra-micronized progesterone in amounts of 100 mg, 150 mg, 200 mg, and 250 mg, though other dose ranges are contemplated herein. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Formulations in accordance with various embodiments may be used to treat or prevent preterm delivery in pregnant women, including in certain women having a shortened cervix. In various embodiments, a capsule, for example a softgel capsule, may be opened and the fill material applied in or around the vagina. However, in various embodiments the capsules are taken orally.

Formulations in accordance with various embodiments may be used to treat or prevent endometrial hyperplasia.

Formulations in accordance with various embodiments may be used to treat or prevent secondary amenorrhea.

Formulations in accordance with various embodiments may be used to mitigate or treat the effects of estradiol supplementation. In particular, formulations in accordance with various embodiments may be co-administered with estradiol and/or co-formulated with estradiol.

Formulations in accordance with various embodiments may be used to treat menopause-related symptoms, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy; and osteoporosis and endometrial hyperplasia reduction.

Additional objects of the present disclosure include: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

Specific Embodiments

Through extensive trial-and-error testing of various fatty acid esters of glycerol and other glycols, embodiments of the invention have been invented that have one or more favorable characteristics for development as a human drug product. Such favorable characteristics include those described above, e.g., improved PK and reduced variability.

Such embodiments include an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical

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ingredient, in micronized form suspended in a carrier that comprises a medium chain fatty acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester.

A more specific such embodiment is such formulation wherein the progesterone is ultramicronized.

In certain such embodiments, the progesterone is suspended and/or solubilized in one or more C6 to C12 fatty acid mono-, di-, or triesters of glycerol, e.g., one or more C6 to C14 triglycerides, e.g., one or more C6 to C12 triglycerides, such as one or more C8-C10 triglycerides. An example of a carrier that provides beneficial properties is C8, C10, or C8 and C10 saturated triglycerides, such as but not limited to MIGLYOL, e.g., MIGLYOL 812.

In such general and more specific embodiments, the non-ionic surfactant is a polyethylene glycol saturated or unsaturated fatty acid ester or diester. In certain such embodiments, the non-ionic surfactant comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol. An example of a non-ionic surfactant that provides beneficial properties is GELUCIRE, e.g., GELUCIRE 44/14.

In certain such embodiments, the non-ionic surfactant has a HLB value of about 15. An illustrative example of such surfactant is GELUCIRE 44/14.

As noted above, such formulations are liquid at room temperature, not gels, hard fats, or any other solid form. The non-ionic surfactant serves to increase viscosity. In some such embodiments, the non-ionic surfactant, e.g., GELUCIRE or TEFOSE, may be solid at room temperature and require melting to effect mixing with the estradiol solubilized in fatty acid-glycol esters but the resultant formulation is advantageously liquid, not solid.

The formulation of such embodiments is typically encapsulated in a soft gelatin capsule or other soft capsule.

Typically, such formulations do not comprise a bioadhesive (i.e., muco-adhesive) agent, a gelling agent, or a dispersing agent, or, at least, do not comprise one or two of such components.

In more specific such formulations, the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant are the only essential ingredients. Non-essential ingredients, e.g., colorants, antioxidants or other preservatives, etc., may, of course, be included but other ingredients in amounts that would materially change the solubility of the progesterone, the PK of the encapsulated formulation, or other clinically relevant properties, e.g., other oils or fatty acid esters, lecithin, muco-adherent agents, gelling agents, dispersing agents, or the like would not be included. Such embodiments of the invention may be described as consisting essentially of the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant, as described in the immediately preceding paragraphs describing illustrative embodiments discovered to have favorable characteristics.

As an example of such embodiments discovered to have such favorable characteristics is mentioned the product identified in Example 2, Table 3, below.

EXAMPLES

Example 1

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 2

Ingredient	mg/ Capsule	%	Function
Ultra-micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

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The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 2

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 3

Ingredient	%	mg/ Capsule	Function
1. Ultra-micronized Progesterone	30.77	200.00	Active
2. Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
3. Lauroyl polyoxy-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
4. Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

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In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

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Example 3

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL, including without limitation MIGLYOL 812, may be used in embodiments comprising a suspension of progesterone.

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As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

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Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg.

TABLE 4

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM	73.4
CAPMUL PG8	95
MIGLYOL 812	27.8
CAPMUL MCM:	86.4
GELUCIRE 44/14 (9:1)	
CAPMUL MCM:	70.5
GELUCIRE 44/14 (7:3)	
CAPMUL MCM:	57.4
GELUCIRE 44/14 (6:3)	

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM in combination with GELUCIRE 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM and GELUCIRE 44/14 system, wherein the ratio of CAPMUL MCM to GELUCIRE 44/14 is 9:1.

TABLE 5

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM:GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM:GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM:GELUCIRE 44/14 (6:4)	57.4

Example 4

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 6

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 7

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/ triglycerides of caprylic/capric acid (CAPMUL MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 8

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 6

Bioavailability Assessment—Fasted

A randomized single-dose oral bioequivalence study comparing 200 mg ultra-micronized progesterone capsule test product (T) and 200 mg PROMETRIUM® (progesterone) capsules (Abbott Laboratories, Abbott Park, Ill.) reference product (R) is conducted. Subjects are administered a single 200 mg dose of either test product (T) or the reference product (R) under fasting conditions, for example, subjects fasted at least 10.0 hours prior to dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose.

Pharmacokinetic measurements are assessed including C_{max} , AUC and optionally T_{max} . Comparative bioavailability of the test product (T) and reference product are assessed.

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Example 7

Bioavailability Assessment—Fed

The procedures for determining bioavailability under fasted conditions are repeated except that subjects are administered a single 200 mg dose of either test product (T) or reference product (R) immediately following a high fat meal, for example, within 30 minutes of dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose. Pharmacokinetic measurements are assessed including C_{max} , AUC and optionally T_{max} . Bioavailability of the test product (T) in reference to the reference product is assessed. The effect of food on the comparative bioavailability of the test product (T) and the reference product (R) are also assessed.

Example 8

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material, i.e. fill mass, preparation 100 is shown. Step 102 comprises mixing a carrier, a lubricant, and an antioxidant as described herein. For example, lecithin and butylated hydroxytoluene may be mixed with one or more medium chain mono-, di- or triglycerides, or combinations thereof mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 104 may comprise mixing ultra-micronized progesterone into the mixture of the carrier, the lubricant, and the antioxidant. A pasty substance is thus formed. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 104 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 106 comprises degassing. The resulting mixture from step 106 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Heating may be performed until the temperature reaches $80^\circ\pm 5^\circ C$.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N_2 . Step 208 comprises degassing. The resulting mixture from step 208 may comprise

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a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to $30^\circ C.\pm 3^\circ C$. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of $55^\circ C.\pm 10^\circ C$. The wedge temperature may be $38^\circ C.\pm 3^\circ C$. The drum cooling temperature may be $4^\circ C.\pm 2^\circ C$. The encapsulator may be lubricated using MIGLYOL 812. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 ± 0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., 650 ± 33 mg and 325 ± 16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Polishing may be performed with isopropyl alcohol.

Example 9

Stability Study

In accordance with various embodiments, formulations in accordance with various embodiments have an exemplary shelf life of 3 months with storage at $25\pm 2^\circ C./60\pm 5\% RH$ in 75 cc HDPE white, opaque bottles with a 38/400 mm white child resistant cap.

Packaging during testing comprises a 75 cc round HDPE bottle and 33 mm cap. A Brasken FPT 300F resin is associated with the cap. Testing criteria include visual appearance, assay of progesterone, dissolution, content uniformity and microbial limits testing.

Three test groups are created. Test group 1 comprises a test at $40^\circ C./75\% RH$. Test group 2 comprises a test at $30^\circ C./65\% RH$. Test group 3 comprises a test at $25^\circ C./60\% RH$. Test group 1 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 1, 2, 3, and 6. Test group 2 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, and 12. Test group 3 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, 12 and 24.

Example 10

A particle size analysis is conducted by using a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the “Beckman Device”). The Beckman Device uses laser diffraction to determine particle size. A sample of a formulation in accordance with various embodiments is provided. The Beckman Device particle sensor yields that the sample has an X50 of 6.67 μm , an X75 of 14.78 μm , and an X25 of 2.193 μm .

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Example 11

A dissolution study was performed using a formulation in accordance with various embodiments. The results of the dissolution study are shown in FIG. 4.

The dissolution study was performed using a United States Pharmacopoeia dissolution apparatus 3 (reciprocating cylinder) ("USP Apparatus 3"). The USP Apparatus 3 was set to 30 dips per minute. Two hundred fifty mL (250 mL) of a solution of 1N HCl with 3% sodium lauryl sulfate was used at 37° C.

FIG. 4 shows dissolution percentage in the y axis over time in minutes on the x axis. A formulation in accordance with various embodiments is shown having circular dots, and is labeled formulation 402. An existing commercial pharmaceutical product containing progesterone is shown having square dots and is labeled existing product 404. As shown in FIG. 4, formulation 402 reaches a higher level of dissolution in a shorter time than existing product 404.

Example 12

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 5.

Example 13

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions. This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
CAPMUL MCM, NF, USP	83.27	582.93
GELUCIRE 44/14, NF	9.29	650
Total	100.00	700

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The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by 10 dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

20 Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

25 Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

30 Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

35 After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

40 All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

45 In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin 50 in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of

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heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of $-70^{\circ}\text{C.} \pm 20^{\circ}\text{C.}$ in the bioanalytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 9, below, for progesterone.

TABLE 9

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean \pm Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	47.0	43.0	81.0 \pm 82.8	117.7 \pm 173.7
AUC _{0-t}	107.6	97.8	163.9 \pm 136.5	191.1 \pm 241.7
AUC _{0-∞}	110.7	110.0	173.5 \pm 143.0	207.1 \pm 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 10, below for progesterone.

TABLE 10

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean \pm Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	2.3	3.0	2.9 \pm 2.3	3.9 \pm 3.4
AUC _{0-t}	8.4	10.9	11.2 \pm 8.7	14.5 \pm 11.0
AUC _{0-∞}	12.9	17.2	15.1 \pm 9.0	19.6 \pm 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to PROMETRIUM.

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Example 14

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of PROMETRIUM and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37°C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from PROMETRIUM. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from PROMETRIUM is attached as FIG. 6.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. The disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad, general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A pharmaceutical composition comprising:
progesterone;
a medium chain oil; and a non-ionic surfactant;
wherein the progesterone is present from about 20 to about 50 weight percent of the composition.
2. The pharmaceutical composition of claim 1, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.
3. The pharmaceutical composition of claim 2, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

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4. The pharmaceutical composition of claim 1, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

5. The pharmaceutical composition of claim 1, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

6. The pharmaceutical composition of claim 1, wherein the composition is provided in a gelatin capsule.

7. The pharmaceutical composition of claim 1, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

8. The pharmaceutical composition of claim 1, wherein progesterone is the sole active ingredient.

9. The pharmaceutical composition of claim 1, wherein the medium chain oil comprises at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

10. The pharmaceutical composition of claim 9, wherein the at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₈ fatty acid mono-, di-, or tri-ester of glycerol.

11. The pharmaceutical composition of claim 10, further comprising a second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol.

12. The pharmaceutical composition of claim 11, wherein the second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₁₀ fatty acid mono-, di-, or tri-ester of glycerol.

13. The pharmaceutical composition of claim 12, wherein the medium chain oil is MIGLYOL 812.

14. A pharmaceutical composition comprising:

75 mg of progesterone;
a medium chain oil; and
a non-ionic surfactant;

wherein the progesterone is present at from about 20 to about 50 weight percent of the composition.

15. The pharmaceutical composition of claim 14, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

16. The pharmaceutical composition of claim 15, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

17. The pharmaceutical composition of claim 14, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

18. The pharmaceutical composition of claim 14, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

19. The pharmaceutical composition of claim 14, wherein the composition is provided in a gelatin capsule.

20. The pharmaceutical composition of claim 14, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

21. The pharmaceutical composition of claim 14, wherein progesterone is the sole active ingredient.

22. The pharmaceutical composition of claim 14, wherein the medium chain oil comprises at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

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23. The pharmaceutical composition of claim 22, wherein the at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₈ fatty acid mono-, di-, or tri-ester of glycerol.

24. The pharmaceutical composition of claim 23, further comprising a second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol.

25. The pharmaceutical composition of claim 24, wherein the second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₁₀ fatty acid mono-, di-, or tri-ester of glycerol.

26. The pharmaceutical composition of claim 25, wherein the medium chain oil is MIGLYOL 812.

27. A pharmaceutical composition comprising:

150 mg progesterone;
a medium chain oil; and
a non-ionic surfactant;

wherein the progesterone is present at from about 20 to about 50 weight percent of the composition.

28. The pharmaceutical composition of claim 27, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

29. The pharmaceutical composition of claim 28, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

30. The pharmaceutical composition of claim 27, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

31. The pharmaceutical composition of claim 27, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

32. The pharmaceutical composition of claim 27, wherein the composition is provided in a gelatin capsule.

33. The pharmaceutical composition of claim 27, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

34. The pharmaceutical composition of claim 27, wherein progesterone is the sole active ingredient.

35. The pharmaceutical composition of claim 27, wherein the medium chain oil comprises at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

36. The pharmaceutical composition of claim 35, wherein the at least one C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₈ fatty acid mono-, di-, or tri-ester of glycerol.

37. The pharmaceutical composition of claim 36, further comprising a second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol.

38. The pharmaceutical composition of claim 37, wherein the second C₆-C₁₄ fatty acid mono-, di-, or tri-ester of glycerol is a C₁₀ fatty acid mono-, di-, or tri-ester of glycerol.

39. The pharmaceutical composition of claim 38, wherein the medium chain oil is MIGLYOL 812.

40. The pharmaceutical composition of claim 27, wherein the medium chain oil is MIGLYOL 812, the non-ionic surfactant is lauroyl polyoxyl-32-glycerides, and wherein the pharmaceutical formulation provides increased progesterone bioavailability compared to a formulation comprising an equivalent amount of micronized progesterone suspended in peanut oil.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,052,386 B2
APPLICATION NO. : 14/125547
DATED : August 21, 2018
INVENTOR(S) : Bernick et al.

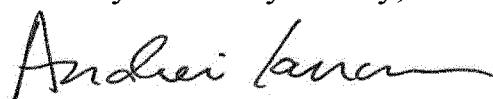
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In Column 10, Line 31, replace “PEG-6-palmitostearate” with -- PEG-6 stearate --.

Signed and Sealed this
Twenty-third Day of July, 2019



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT L



US010206932B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 10,206,932 B2
(45) **Date of Patent:** *Feb. 19, 2019

- (54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**
- (71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)
- (72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US); **Peter H. R. Persicaner**, Boca Raton, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)
- (73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 78 days.
- This patent is subject to a terminal disclaimer.
- (21) Appl. No.: **14/719,933**
- (22) Filed: **May 22, 2015**
- (65) **Prior Publication Data**
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3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	6/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopflin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	8/1977	Higuchi et al.
4,071,623 A	1/1978	van der Vies
4,093,709 A	6/1978	Choi et al.
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong
4,237,885 A	12/1980	Wong et al.
4,310,510 A	1/1982	Sherman et al.
4,327,725 A	5/1982	Cortese et al.
4,372,951 A	2/1983	Vorys
4,384,096 A	5/1983	Sonnabend
4,393,871 A	7/1983	Vorhauer et al.
4,402,695 A	9/1983	Wong
4,423,151 A	12/1983	Baranczuk
4,449,980 A	5/1984	Millar et al.
4,610,687 A	9/1986	Fogwell
4,629,449 A	12/1986	Wong
4,732,763 A	3/1988	Beck et al.
4,738,957 A	4/1988	Laurent et al.

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI1001367-9 A2	7/2012
CA	2612380	12/2006

(Continued)

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| <i>A61K 9/10</i> | (2006.01) |
| <i>A61K 31/57</i> | (2006.01) |
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- (52) **U.S. Cl.**
- CPC *A61K 31/565* (2013.01); *A61K 9/10* (2013.01); *A61K 9/4858* (2013.01); *A61K 31/57* (2013.01)

- (58) **Field of Classification Search**
- None
- See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	1/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson

OTHER PUBLICATIONS

- US 6,214,374, 04/2001, Schmirler et al. (withdrawn)
- Pachman et al., "Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions," International Journal of Women's Health, May 7, 2010.*
- U.S. Appl. No. 13/684,002, filed Nov. 21, 2012, U.S. Pat. No. 8,633,178, Jan. 21, 2014.
- U.S. Appl. No. 13/843,362, filed Mar. 15, 2013.
- U.S. Appl. No. 13/843,428, filed Mar. 15, 2013, U.S. Pat. No. 9,301,920, Apr. 5, 2016.

(Continued)

Primary Examiner — Jared Barsky(74) *Attorney, Agent, or Firm — Kilpatrick Townsend & Stockton LLP*(57) **ABSTRACT**

Pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent comprising a medium chain (C6-C12) oil.

US 10,206,932 B2

Page 2

(56)	References Cited					
U.S. PATENT DOCUMENTS						
4,756,907 A	7/1988	Beck et al.	5,762,614 A	6/1998	Caillouette	
4,762,717 A	8/1988	Crowley, Jr.	5,770,176 A	6/1998	Nargessi	
4,788,062 A	11/1988	Gale et al.	5,770,219 A	6/1998	Chiang et al.	
4,816,257 A	3/1989	Buster et al.	5,770,220 A	6/1998	Meconi	
4,822,616 A	4/1989	Zimmermann et al.	5,770,227 A	6/1998	Dong	
4,865,848 A	9/1989	Cheng et al.	5,776,495 A	7/1998	Duclos et al.	
4,900,734 A	2/1990	Maxson et al.	5,780,044 A	7/1998	Tipton	
4,906,475 A	3/1990	Kim	5,780,050 A	7/1998	Jain	
4,942,158 A	7/1990	Sarpotdar et al.	5,788,980 A	8/1998	Nabahi	
4,961,931 A	10/1990	Wong	5,788,984 A	8/1998	Schmidt	
5,030,629 A	7/1991	Rajadhyaksha	5,789,442 A	8/1998	Garfield et al.	
5,064,654 A	11/1991	Berner et al.	5,811,416 A	9/1998	Chwalisz et al.	
5,108,995 A	4/1992	Casper	5,811,547 A	9/1998	Nalcamichi et al.	
5,128,138 A	7/1992	Blank	5,814,329 A	9/1998	Shah	
5,130,137 A	7/1992	Crowley, Jr.	5,820,878 A	10/1998	Shimamura	
5,140,021 A	8/1992	Maxson et al.	5,827,200 A	10/1998	Caillouette	
5,164,416 A	11/1992	Nagai et al.	5,840,327 A	11/1998	Gale	
5,211,952 A	5/1993	Spicer	5,843,468 A	12/1998	Yum	
5,252,334 A	10/1993	Chiang et al.	5,843,979 A	12/1998	Wille	
5,280,023 A	1/1994	Ehrlich et al.	5,858,394 A	1/1999	Lipp	
5,288,496 A	2/1994	Lewis	5,863,552 A	1/1999	Yue	
5,340,584 A	8/1994	Spicer et al.	5,866,603 A	2/1999	Li et al.	
5,340,585 A	8/1994	Pike et al.	5,869,084 A	2/1999	Paradissis et al.	
5,340,586 A	8/1994	Pike et al.	5,882,676 A	3/1999	Yum	
5,362,497 A	8/1994	Yamada et al.	5,885,612 A	3/1999	Meconi	
5,382,573 A	1/1995	Casper	5,888,533 A	3/1999	Dunn	
5,393,528 A	2/1995	Staab	5,891,462 A	4/1999	Carrara	
5,393,529 A	2/1995	Hoffmann et al.	5,891,868 A	4/1999	Cummings et al.	
5,419,910 A	5/1995	Lewis	5,898,038 A	4/1999	Yallampalli et al.	
5,468,736 A	11/1995	Hodgen	5,902,603 A	5/1999	Chen	
5,474,783 A	12/1995	Miranda et al.	5,904,931 A	5/1999	Gunther	
5,480,776 A	1/1996	Dullien	5,906,830 A	5/1999	Farinas	
5,514,673 A	5/1996	Heckenmueller et al.	5,912,010 A	6/1999	Wille	
5,516,528 A	5/1996	Hughes et al.	5,916,176 A	6/1999	Caillouette	
5,527,534 A	6/1996	Myhling	RE36,247 E	7/1999	Plunkett et al.	
5,529,782 A	6/1996	Staab	5,919,477 A	7/1999	Bevan	
5,538,736 A	7/1996	Barth	5,922,349 A	7/1999	Elliesen et al.	
5,543,150 A	8/1996	Bologna et al.	5,928,666 A	7/1999	Farinas et al.	
5,547,948 A	8/1996	Barcomb	5,942,243 A	8/1999	Shah	
5,556,635 A	9/1996	Grognet	5,942,531 A	8/1999	Diaz et al.	
5,565,199 A	10/1996	Page et al.	5,952,000 A	9/1999	Fikstad	
5,567,831 A	10/1996	Li	5,958,446 A	9/1999	Miranda et al.	
5,569,652 A	10/1996	Beier et al.	5,962,445 A	10/1999	Stewart	
5,580,572 A	12/1996	Liorzou	5,968,919 A	10/1999	Gyurik	
5,582,592 A	12/1996	Kendrick	5,972,372 A	10/1999	Saleh et al.	
5,585,370 A	12/1996	Casper	5,985,311 A	11/1999	Cordes	
5,595,759 A	1/1997	Wright et al.	5,985,850 A	11/1999	Falk	
5,595,970 A	1/1997	Garfield et al.	5,985,861 A	11/1999	Levine et al.	
5,605,702 A	2/1997	Math	5,993,856 A	11/1999	Ragavan et al.	
5,607,691 A	3/1997	Solas	5,989,568 A	12/1999	De Lacharriere	
5,607,693 A	3/1997	Bonte	6,001,846 A	12/1999	Edwards et al.	
5,609,617 A	3/1997	Cady	6,007,835 A	12/1999	Bon Lapillonne et al.	
5,620,705 A	4/1997	Dong et al.	6,010,715 A	1/2000	Pollock	
5,626,866 A	5/1997	Heiber	6,013,276 A	1/2000	Teillaud	
5,629,021 A	5/1997	Wright	6,022,562 A	2/2000	Autant et al.	
5,633,011 A	5/1997	Dong et al.	6,024,974 A	2/2000	Li	
5,633,242 A	5/1997	Oettel et al.	6,024,976 A	2/2000	Miranda et al.	
5,639,743 A	6/1997	Kaswan et al.	6,028,057 A	2/2000	Burns	
5,653,983 A	8/1997	Bonte	6,030,948 A	2/2000	Mann	
5,656,286 A	8/1997	Miranda et al.	6,039,968 A	3/2000	Nabahi	
5,660,839 A	8/1997	Allec	6,040,340 A	3/2000	Garfield	
5,662,927 A	9/1997	Ehrlich	6,056,972 A	5/2000	Hermsmeyer	
5,663,160 A	9/1997	Dumas	6,060,077 A	5/2000	Meignant	
5,676,968 A	10/1997	Lipp et al.	6,068,853 A	5/2000	Berner	
5,677,292 A	10/1997	Li et al.	6,074,625 A	6/2000	Hawthorne et al.	
5,686,097 A	11/1997	Crisologo	6,077,531 A	6/2000	Salin-Drouin	
5,693,335 A	12/1997	Xia	6,080,118 A	6/2000	Blythe	
5,694,947 A	12/1997	Lehtinen et al.	6,083,178 A	7/2000	Caillouette	
5,700,480 A	12/1997	Hille et al.	6,086,916 A	7/2000	Agnus et al.	
5,709,844 A	1/1998	Arbeit et al.	6,087,352 A	7/2000	Trout	
5,719,197 A	2/1998	Mantelle	6,090,404 A	7/2000	Meconi et al.	
5,735,801 A	4/1998	Caillouette	6,096,338 A	7/2000	Lacy et al.	
5,739,176 A	4/1998	Dunn et al.	6,106,848 A	8/2000	Willcox	
5,744,463 A	4/1998	Bair	6,117,446 A	9/2000	Place	
5,747,058 A	5/1998	Tipton et al.	6,117,450 A	9/2000	Dittgen et al.	
			6,124,362 A	9/2000	Bradbury	
			6,133,251 A	10/2000	Dittgen et al.	
			6,133,320 A	10/2000	Yallampalli et al.	
			6,139,868 A	10/2000	Hoffmann	

US 10,206,932 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

6,139,873 A	10/2000	Hughes, Jr. et al.	6,548,053 B1	4/2003	Murray
6,149,935 A	11/2000	Tenzel	6,548,491 B2	4/2003	Tanabe et al.
6,153,216 A	11/2000	Cordes et al.	6,551,611 B2	4/2003	Elliesen et al.
6,165,491 A	12/2000	Grasset et al.	6,555,131 B1	4/2003	Wolff
6,165,975 A	12/2000	Adams et al.	6,562,367 B1	5/2003	Wolff
6,187,323 B1	2/2001	Aiache et al.	6,562,370 B2	5/2003	Luo
6,187,339 B1	2/2001	de Haan et al.	6,562,790 B2	5/2003	Chein
6,190,331 B1	2/2001	Caillouette	6,569,463 B2	5/2003	Patel et al.
6,201,072 B1	3/2001	Rathi et al.	6,583,129 B1	6/2003	Mazer et al.
6,217,886 B1	4/2001	Rubinstein	6,586,006 B2	7/2003	Roser et al.
6,225,297 B1	5/2001	Stockemann	6,589,549 B2	7/2003	Shih et al.
6,227,202 B1	5/2001	Matapurkar	6,593,317 B1	7/2003	de Ziegler et al.
6,228,383 B1	5/2001	Hansen	6,599,519 B1	7/2003	Seo
6,228,852 B1	5/2001	Shaak	6,610,652 B2	8/2003	Adams et al.
6,242,509 B1	6/2001	MacQueen	6,610,670 B2	8/2003	Bleckensfeld et al.
6,245,811 B1	6/2001	Horrobin	6,610,674 B1	8/2003	Schreiber
6,262,115 B1	7/2001	Guittard et al.	6,635,274 B1	10/2003	Carter
6,267,984 B1	7/2001	Hamlin	6,638,528 B1	10/2003	Kanios
6,274,165 B1	8/2001	Meconi	6,638,536 B2	10/2003	Savoir et al.
6,277,418 B1	8/2001	Marakverich et al.	6,645,528 B1	11/2003	Straub et al.
6,283,927 B1	9/2001	Caillouette	6,649,155 B1	11/2003	Dunlop
6,287,588 B1	9/2001	Shih et al.	6,653,298 B2	11/2003	Potter et al.
6,287,693 B1	9/2001	Savoir et al.	6,656,929 B1	12/2003	Agnus et al.
6,294,188 B1	9/2001	Ragavan et al.	6,660,726 B2	12/2003	Hill et al.
6,294,192 B1	9/2001	Patel et al.	6,663,608 B2	12/2003	Rathbone et al.
6,294,550 B1	9/2001	Place et al.	6,663,895 B2	12/2003	Savoir et al.
6,299,900 B1	10/2001	Reed et al.	6,682,757 B1	1/2004	Wright
6,303,132 B1	10/2001	Nelson	6,692,763 B1	2/2004	Cummings et al.
6,303,588 B1	10/2001	Danielov	6,708,822 B1	3/2004	Muni
6,306,841 B1	10/2001	Place et al.	6,720,001 B2	4/2004	Chen
6,306,914 B1	10/2001	de Ziegler et al.	6,737,081 B2	5/2004	Savoir et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,740,333 B2	5/2004	Beckett et al.
6,309,848 B1	10/2001	Howett et al.	6,743,448 B2	6/2004	Kryger
6,312,703 B1	11/2001	Orthoefer	6,743,815 B2	6/2004	Huebner et al.
6,328,987 B1	12/2001	Marini	6,747,018 B2	6/2004	Tanabe et al.
6,342,491 B1	1/2002	Dey et al.	6,750,291 B2	6/2004	Kim
6,344,211 B1	2/2002	Hille	6,756,208 B2	6/2004	Griffin et al.
6,372,209 B1	4/2002	Chrisope	6,781,524 B2	11/2004	Marini
6,372,245 B1	4/2002	Vo	6,841,716 B1	1/2005	Tsutsumi
6,372,246 B1	4/2002	Wei et al.	6,844,334 B2	1/2005	Hill et al.
6,387,390 B1	5/2002	Deaver et al.	6,855,703 B1	2/2005	Hill et al.
6,402,705 B1	6/2002	Caillouette	6,860,859 B2	3/2005	Mehrotra et al.
6,416,778 B1	7/2002	Ragavan et al.	6,866,865 B2	3/2005	Hsia et al.
6,420,352 B1	7/2002	Knowles	6,869,969 B2	3/2005	Heubner et al.
6,423,039 B1	7/2002	Rathbone et al.	6,878,518 B2	4/2005	Whitehead
6,423,683 B1	7/2002	Heaton et al.	6,901,278 B1	5/2005	Notelovitz
6,432,438 B1	8/2002	Shukla	6,905,705 B2	6/2005	Palm et al.
6,436,633 B1	8/2002	Kreider et al.	6,911,211 B2	6/2005	Tamarkin
6,440,454 B1	8/2002	Santoro et al.	6,911,438 B2	6/2005	Wright
6,444,224 B1	9/2002	Rathbone et al.	6,923,988 B2	8/2005	Patel et al.
6,444,234 B1	9/2002	Kirby et al.	6,924,274 B2	8/2005	Lardy et al.
6,451,300 B1	9/2002	Leyba	6,932,983 B1	8/2005	Straub et al.
6,451,339 B2	9/2002	Patel et al.	6,939,558 B2	9/2005	Massara et al.
6,451,779 B1	9/2002	Hesch	6,943,021 B2	9/2005	Klausner et al.
6,455,246 B1	9/2002	Howett et al.	6,958,327 B1	10/2005	Hillisch et al.
6,455,517 B1	9/2002	Tanabe et al.	6,960,337 B2	11/2005	Pike
6,465,004 B1	10/2002	Houze	6,962,691 B1	11/2005	Lulla et al.
6,465,005 B1	10/2002	Biali	6,962,908 B2	11/2005	Aloba et al.
6,465,006 B1	10/2002	Zhang	6,967,194 B1	11/2005	Matsuo et al.
6,468,526 B2	10/2002	Chrisope	6,974,569 B2	12/2005	Boyd
6,469,016 B1	10/2002	Place et al.	6,977,250 B2	12/2005	Rodriguez
6,472,434 B1	10/2002	Place et al.	6,978,945 B2	12/2005	Wong et al.
6,479,232 B1	11/2002	Howett et al.	6,995,149 B1	2/2006	Reilhac
6,495,160 B2	12/2002	Esposito	7,004,321 B1	2/2006	Hackbarth
6,500,814 B1	12/2002	Hesch	7,005,429 B2	2/2006	Dey et al.
6,503,896 B1	1/2003	Tanabe et al.	7,011,846 B2	3/2006	Shojaei et al.
6,511,969 B1	1/2003	Hermsmeyer	7,018,992 B2	3/2006	Koch et al.
6,521,250 B2	2/2003	Seibertz	7,030,104 B2	4/2006	Paris
6,526,980 B1	3/2003	Tracy et al.	7,030,157 B2	4/2006	Ke et al.
6,528,094 B1	3/2003	Savoir et al.	RE39,104 E	5/2006	Duclos et al.
6,531,149 B1	3/2003	Meconi	7,074,779 B2	7/2006	Sui et al.
6,537,580 B1	3/2003	Savoir et al.	7,083,590 B1	8/2006	Bunt et al.
6,538,039 B2	3/2003	Laurent	7,091,213 B2	8/2006	Metcalf, III et al.
6,544,196 B2	4/2003	Caillouette	7,094,228 B2	8/2006	Zhang
6,544,553 B1	4/2003	Hsia et al.			

US 10,206,932 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
7,097,853 B1	8/2006	Keister	7,945,459 B2	5/2011	Grace et al.	
7,101,342 B1	9/2006	Caillouette	7,960,368 B2	6/2011	Rao	
7,105,573 B2	9/2006	Krajcik	7,989,436 B2	8/2011	Hill et al.	
7,135,190 B2	11/2006	Piao et al.	7,989,487 B2	8/2011	Welsh et al.	
7,153,522 B1	12/2006	Ikeura	8,022,053 B2	9/2011	Mueller et al.	
7,163,681 B2	1/2007	Giles-Komar et al.	8,048,017 B2	11/2011	Xu	
7,163,699 B2	1/2007	Besse	8,048,869 B2	11/2011	Bunschoten et al.	
7,175,850 B2	2/2007	Cevc	8,063,030 B2	11/2011	Ellman	
7,179,799 B2	2/2007	Hill et al.	8,071,576 B2	12/2011	Visser	
7,196,074 B2	3/2007	Blye et al.	8,076,317 B2	12/2011	Kulmann	
7,198,800 B1	4/2007	Ko	8,076,319 B2	12/2011	Leonard	
7,198,801 B2	4/2007	Carrara et al.	8,080,553 B2	12/2011	Auspitz	
7,226,910 B2	6/2007	Wilson et al.	8,088,605 B2	1/2012	Beudet et al.	
7,247,625 B2	7/2007	Zhang et al.	8,096,940 B2	1/2012	Iverson	
7,250,446 B2	7/2007	Sangita et al.	8,101,209 B2	1/2012	Legrand et al.	
7,267,829 B2	9/2007	Kirby et al.	8,101,773 B2	1/2012	Smith et al.	
7,300,926 B2	11/2007	Prokai et al.	8,114,152 B2	2/2012	Furst	
7,303,763 B2	12/2007	Ho	8,114,434 B2	2/2012	Sasaki et al.	
7,317,037 B2	1/2008	Fensome et al.	8,114,442 B2	2/2012	Tucker	
7,329,654 B2	2/2008	Kanojia et al.	8,119,741 B2	2/2012	Pavlin	
7,335,650 B2	2/2008	Potter et al.	8,121,886 B2	2/2012	Azar	
7,374,779 B2	5/2008	Chen et al.	8,124,118 B2	2/2012	Lennernaes	
7,378,404 B2	5/2008	Peters et al.	8,124,595 B2	2/2012	Boissonneault	
7,381,427 B2	6/2008	Ancira	8,147,561 B2	4/2012	Binmoeller	
7,387,789 B2	6/2008	Klose et al.	8,148,546 B2	4/2012	Baasner	
7,388,006 B2	6/2008	Schmees et al.	8,158,613 B2	4/2012	Staniforth	
7,414,043 B2	8/2008	Kosemund et al.	8,158,614 B2	4/2012	Lambert et al.	
7,427,413 B2	9/2008	Savoir et al.	8,163,722 B2	4/2012	Savor	
7,427,609 B2	9/2008	Leonard	8,177,449 B2	5/2012	Watkinson	
7,429,576 B2	9/2008	Labrie	8,182,833 B2	5/2012	Hermsmeyer	
7,431,941 B2	10/2008	Besins et al.	8,187,615 B2	5/2012	Friedman	
7,456,159 B2	11/2008	Houze	8,187,640 B2	5/2012	Dunn	
7,459,445 B2	12/2008	Hill et al.	8,195,403 B2	6/2012	Wood, Jr.	
7,465,587 B2	12/2008	Imrich	8,202,736 B2	6/2012	Mousa et al.	
7,470,433 B2	12/2008	Carrara et al.	8,217,024 B2	7/2012	Ahmed et al.	
7,485,666 B2	2/2009	Villaneuva et al.	8,221,785 B2	7/2012	Chien	
7,497,855 B2	3/2009	Ausiello et al.	8,222,008 B2	7/2012	Thoene	
7,498,303 B2	3/2009	Arnold	8,222,237 B2	7/2012	Narkunan	
7,534,765 B2	5/2009	Gregg et al.	8,227,454 B2	7/2012	Hill et al.	
7,534,780 B2	5/2009	Ring	8,227,509 B2	7/2012	Castro et al.	
7,550,142 B2	6/2009	Giles-Komar et al.	8,241,664 B2	8/2012	Dudley et al.	
7,563,565 B1	7/2009	Matsuo et al.	8,247,393 B2	8/2012	Ahmed et al.	
7,569,274 B2	8/2009	Alphonse	8,257,724 B2	9/2012	Cromack	
7,572,779 B2	8/2009	Aloba et al.	8,257,725 B2	9/2012	Cromack	
7,572,780 B2	8/2009	Hermsmeyer	8,268,352 B2	9/2012	Karan	
7,589,082 B2	9/2009	Savoir et al.	8,268,806 B2	9/2012	Labrie	
7,671,027 B2	3/2010	Loumaye	8,268,878 B2	9/2012	Johnson	
7,674,783 B2	3/2010	Hermsmeyer	8,273,730 B2	9/2012	Fernandez et al.	
7,687,281 B2	3/2010	Roth et al.	8,287,888 B2	10/2012	Song et al.	
7,687,485 B2	3/2010	Levinson et al.	8,288,366 B2	10/2012	Gonzalez	
7,694,683 B2	4/2010	Callister et al.	8,318,898 B2	11/2012	Fasel	
7,704,983 B1	4/2010	Hodgen et al.	8,324,193 B2	12/2012	Sepsick	
7,727,720 B2	6/2010	Dhallan	8,329,680 B2	12/2012	Evans et al.	
7,732,408 B2	6/2010	Josephson et al.	8,337,814 B2	12/2012	Osbakken	
7,749,989 B2	7/2010	Hill et al.	8,344,007 B2	1/2013	Chui	
7,767,656 B2	8/2010	Shoichet et al.	8,349,820 B2	1/2013	Zeun et al.	
7,799,769 B2	9/2010	White	8,353,863 B2	1/2013	Imran	
7,815,936 B2	10/2010	Hasenzahl	8,357,723 B2	1/2013	Satyam	
7,815,949 B2	10/2010	Cohen	8,361,995 B2	1/2013	Schramm	
7,829,115 B2	11/2010	Besins et al.	8,362,091 B2	1/2013	Besonov	
7,829,116 B2	11/2010	Frye	8,372,424 B2	2/2013	Berry	
RE42,012 E	12/2010	Deaver et al.	8,372,806 B2	2/2013	Bragagna	
7,850,992 B2	12/2010	Hwang, II	8,377,482 B2	2/2013	Laurie	
7,854,753 B2	12/2010	Kraft	8,377,994 B2	2/2013	Drechsler	
7,858,607 B2	12/2010	Mamchur	8,394,759 B2	3/2013	Barathur	
RE42,072 E	1/2011	Deaver et al.	8,415,332 B2	4/2013	Reape	
7,862,552 B2	1/2011	McIntyre et al.	8,420,111 B2	4/2013	Hermsmeyer	
7,867,990 B2	1/2011	Schultz et al.	8,435,561 B2	5/2013	Besins et al.	
7,871,643 B2	1/2011	Lizio	8,435,972 B2	5/2013	Sayeed	
7,879,830 B2	2/2011	Wiley	8,449,879 B2	5/2013	Applegate	
7,884,093 B2	2/2011	Creasy et al.	8,450,108 B2	5/2013	Boyce	
7,925,519 B2	4/2011	Greene	8,454,945 B2	6/2013	Narain	
7,939,104 B2	5/2011	Barbera et al.	8,455,468 B2	6/2013	Kellermann	
7,943,602 B2	5/2011	Bunschoten et al.	8,461,138 B2	6/2013	Boissonneault	
7,943,604 B2	5/2011	Coelingh Bennink et al.	8,476,252 B2	7/2013	Pickersgill	
			8,481,488 B2	7/2013	Carter	

US 10,206,932 B2

Page 5

(56)	References Cited				
U.S. PATENT DOCUMENTS					
8,486,374 B2	7/2013 Zlatkis	2002/0058926 A1	5/2002 Rathbone et al.		
8,486,442 B2	7/2013 Yamaji	2002/0064541 A1	5/2002 Lapidot et al.		
8,492,368 B2	7/2013 Lewandowski	2002/0076441 A1	6/2002 Shih et al.		
8,507,467 B2	8/2013 Ueda	2002/0102308 A1	8/2002 Wei et al.		
8,512,693 B2	8/2013 Azevedo	2002/0107230 A1	8/2002 Waldon et al.		
8,512,754 B2	8/2013 Needham	2002/0114803 A1	8/2002 Deaver et al.		
8,518,376 B2	8/2013 Schuz	2002/0119174 A1	8/2002 Gardlik		
8,536,159 B2	9/2013 Zeng	2002/0119198 A1	8/2002 Gao		
8,540,967 B2	9/2013 Trivedi	2002/0132801 A1	9/2002 Heil et al.		
8,541,400 B2	9/2013 Joabsson	2002/0137749 A1	9/2002 Levinson et al.		
8,551,462 B2	10/2013 Marenus	2002/0142017 A1	10/2002 Simonnet		
8,551,508 B2	10/2013 Lee et al.	2002/0151530 A1	10/2002 Leonard et al.		
8,557,281 B2	10/2013 Tuominen	2002/0156394 A1	10/2002 Mehrotra et al.		
8,568,374 B2	10/2013 De Graaff	2002/0169150 A1	11/2002 Pickar		
8,591,951 B2	11/2013 Kohn	2002/0169205 A1	11/2002 Garfield		
8,613,951 B2	12/2013 Troiano	2002/0173510 A1	11/2002 Levinson et al.		
8,633,178 B2	1/2014 Cacace	2002/0193356 A1	12/2002 Van Beek et al.		
8,633,180 B2	1/2014 Zeng	2002/0193758 A1	12/2002 Sandberg		
8,636,787 B2	1/2014 Sabaria	2002/0197286 A1	12/2002 Brandman		
8,636,982 B2	1/2014 Schuz	2003/0003139 A1	1/2003 Gunther		
8,653,129 B2	2/2014 Fein	2003/0004145 A1	1/2003 Leonard		
8,658,627 B2	2/2014 Voskuhl	2003/0007994 A1	1/2003 Bunt et al.		
8,658,628 B2	2/2014 Baucom	2003/0027772 A1	2/2003 Breton		
8,663,681 B2	3/2014 Ahmed et al.	2003/0091620 A1	2/2003 Venkateshwaran		
8,663,692 B1	3/2014 Mueller	2003/0044453 A1	3/2003 Volkel		
8,663,703 B2	3/2014 Moldavski	2003/0049307 A1	3/2003 Gyurik		
8,664,207 B2	3/2014 Zheng	2003/0064097 A1	4/2003 Patel et al.		
8,669,293 B2	3/2014 Sharoni	2003/0064975 A1	4/2003 Koch et al.		
8,679,552 B2	3/2014 Guthery	2003/0072760 A1	4/2003 Sirbasku		
8,694,358 B2	4/2014 Tryfon	2003/0073248 A1	4/2003 Roth et al.		
8,697,127 B2	4/2014 Sah	2003/0077367 A1	4/2003 Hesch		
8,697,710 B2	4/2014 Zeng	2003/0077297 A1 *	4/2003 Chen A61K 9/1617		
8,703,105 B2	4/2014 Besonov		424/400		
8,709,385 B2	4/2014 Schuz	2003/0078245 A1	4/2003 Bennink et al.		
8,709,451 B2	4/2014 Rapoport	2003/0091640 A1	5/2003 Ramanathan et al.		
8,715,735 B2	5/2014 Funke	2003/0092691 A1	5/2003 Besse et al.		
8,721,331 B2	5/2014 Raghuprasad	2003/0096012 A1	5/2003 Besse et al.		
8,722,021 B2	5/2014 Eini	2003/0104048 A1	6/2003 Patel et al.		
8,734,846 B2	5/2014 Hrkach	2003/0109507 A1	6/2003 Beckmann		
8,735,381 B2	5/2014 Podolski	2003/0113268 A1	6/2003 Buenafae		
8,741,336 B2	6/2014 Dipierro	2003/0114420 A1	6/2003 Salvati et al.		
8,741,373 B2	6/2014 Rao	2003/0114430 A1	6/2003 MacLeod et al.		
8,753,661 B2	6/2014 Gassner	2003/0124182 A1	7/2003 Shojaei et al.		
8,784,882 B2	7/2014 Mattern	2003/0124191 A1	7/2003 Besse et al.		
8,846,648 B2	9/2014 Bernick et al.	2003/0130558 A1	7/2003 Massara et al.		
8,846,649 B2	9/2014 Bernick et al.	2003/0144258 A1	7/2003 Heil et al.		
8,933,059 B2	1/2015 Bernick et al.	2003/0157157 A1	8/2003 Luo et al.		
8,987,237 B2	3/2015 Bernick et al.	2003/0166509 A1	9/2003 Edwards et al.		
8,987,238 B2	3/2015 Bernick et al.	2003/0170295 A1	9/2003 Yoon		
8,993,548 B2	3/2015 Bernick et al.	2003/0175329 A1	9/2003 Mak		
8,993,549 B2	3/2015 Bernick et al.	2003/0175333 A1	9/2003 Shefer		
9,006,222 B2	4/2015 Bernick et al.	2003/0180352 A1	9/2003 Patel et al.		
9,012,434 B2	4/2015 Bernick et al.	2003/0181353 A1	9/2003 Nyce		
9,114,145 B2	8/2015 Bernick et al.	2003/0181728 A1	9/2003 Salvati et al.		
9,114,146 B2	8/2015 Bernick et al.	2003/0191096 A1	10/2003 Leonard et al.		
9,180,091 B2	11/2015 Bernick et al.	2003/0195177 A1	10/2003 Leonard et al.		
9,248,136 B2	2/2016 Bernick et al.	2003/0215496 A1	11/2003 Patel et al.		
9,289,382 B2	3/2016 Bernick et al.	2003/0219402 A1	11/2003 Rutter		
9,301,920 B2	4/2016 Bernick et al.	2003/0220297 A1	11/2003 Bernstein et al.		
2001/0005728 A1	2/2001 Guittard et al.	2003/0224057 A1	12/2003 Martin-Letellier et al.		
2001/0009673 A1	7/2001 Gunther	2003/0224059 A1	12/2003 Lerner et al.		
2001/0021816 A1	9/2001 Caillouette	2003/0225047 A1	12/2003 Friedman		
2001/0023261 A1	9/2001 Ryoo	2003/0225048 A1	12/2003 Friedman		
2001/0027189 A1	10/2001 Bennink et al.	2003/0225050 A1	12/2003 Eichardt et al.		
2001/0029357 A1	10/2001 Bunt et al.	2003/0228686 A1	12/2003 Klausner et al.		
2001/0031747 A1	10/2001 de Ziegler et al.	2003/0229057 A1	12/2003 Caubel et al.		
2001/0032125 A1	10/2001 Bhan et al.	2003/0235596 A1	12/2003 Gao		
2001/0034340 A1	10/2001 Pickar	2003/0236236 A1	12/2003 Chen et al.		
2001/0053383 A1	12/2001 Sablotsky	2004/0009960 A1	1/2004 Heil et al.		
2001/0056068 A1	12/2001 Chwalisz et al.	2004/0022820 A1	2/2004 Anderson		
2002/0012710 A1	1/2002 Lansky	2004/0034001 A1	2/2004 Karara		
2002/0026158 A1	2/2002 Rathbone et al.	2004/0037881 A1	2/2004 Guittard et al.		
2002/0028788 A1	3/2002 Bunt et al.	2004/0039356 A1	2/2004 Maki		
2002/0035070 A1	3/2002 Gardlik	2004/0043043 A1	3/2004 Schlyter		
2002/0058648 A1	5/2002 Hammerly	2004/0043943 A1	3/2004 Guittard et al.		
		2004/0044080 A1	3/2004 Place et al.		
		2004/0048900 A1	3/2004 Flood		
		2004/0052824 A1	3/2004 Abou Chakra-Vemet et al.		
		2004/0073024 A1	4/2004 Metcalf, III et al.		

US 10,206,932 B2

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(56)

References Cited**U.S. PATENT DOCUMENTS**

2004/0077605 A1	4/2004	Salvati et al.	2005/0244522 A1	11/2005	Carrara et al.
2004/0077606 A1	4/2004	Salvati et al.	2005/0245902 A1	11/2005	Cornish et al.
2004/0087548 A1	5/2004	Salvati et al.	2005/0250746 A1	11/2005	Iammatteo
2004/0087564 A1	5/2004	Wright	2005/0250750 A1	11/2005	Cummings et al.
2004/0089308 A1	5/2004	Welch	2005/0250753 A1	11/2005	Fink et al.
2004/0092494 A9	5/2004	Dudley	2005/0256028 A1	11/2005	Yun et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0266078 A1	11/2005	Jorda et al.
2004/0093261 A1	5/2004	Jain et al.	2005/0266088 A1	12/2005	Frijlink
2004/0097468 A1	5/2004	Wimalawansa	2005/0271597 A1	12/2005	Keith
2004/0101557 A1	5/2004	Gibson et al.	2005/0271598 A1	12/2005	Friedman et al.
2004/0106542 A1	6/2004	Deaver et al.	2005/0272685 A1	12/2005	Hung
2004/0110732 A1	6/2004	Masini	2005/0272712 A1	12/2005	Grubb et al.
2004/0131670 A1	7/2004	Gao	2006/0009428 A1	1/2006	Grubb
2004/0138103 A1	7/2004	Patt	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0142012 A1	7/2004	Bunt et al.	2006/0018937 A1	1/2006	Friedman et al.
2004/0146539 A1	7/2004	Gupta	2006/0019978 A1	1/2006	Balog
2004/0146894 A1	7/2004	Warrington et al.	2006/0020002 A1	1/2006	Salvati et al.
2004/0147578 A1	7/2004	Calvet	2006/0030615 A1	2/2006	Fensome et al.
2004/0161435 A1	8/2004	Gupta	2006/0034889 A1	2/2006	Jo et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0034904 A1	2/2006	Weimann
2004/0176336 A1	9/2004	Rodriguez	2006/0040904 A1	2/2006	Ahmed et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0191207 A1	9/2004	Lipari	2006/0052341 A1	3/2006	Cornish et al.
2004/0191276 A1	9/2004	Muni	2006/0069031 A1	3/2006	Loumaye
2004/0198706 A1	10/2004	Carrara et al.	2006/0078618 A1	4/2006	Constantinides
2004/0210280 A1	10/2004	Liedtke	2006/0083778 A1	4/2006	Allison et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0084704 A1	4/2006	Shih
2004/0219124 A1	11/2004	Gupta	2006/0088580 A1	4/2006	Seibertz
2004/0225140 A1	11/2004	Sciano	2006/0089337 A1	4/2006	Casper et al.
2004/0234606 A1	11/2004	Levine et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0241219 A1	12/2004	Hille	2006/0100180 A1	5/2006	Bohlmann
2004/0243437 A1	12/2004	Grace et al.	2006/0106004 A1	5/2006	Brody et al.
2004/0253319 A1	12/2004	Netke et al.	2006/0110415 A1	5/2006	Gupta
2004/0259817 A1	12/2004	Waldon et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0121102 A1	6/2006	Chiang
2005/0003003 A1	1/2005	Deaver	2006/0121626 A1	6/2006	Imrich
2005/0004088 A1	1/2005	Hesch	2006/0134188 A1	6/2006	Podhaisky et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2006/0135619 A1	6/2006	Kick et al.
2005/0014729 A1	1/2005	Pulaski	2006/0165744 A1	7/2006	Anyarambhatla
2005/0020550 A1	1/2005	Latif	2006/0193789 A1	8/2006	Tamarkin
2005/0020552 A1	1/2005	Aschkenasay et al.	2006/0194775 A1	8/2006	Tofovic et al.
2005/0021009 A1	1/2005	Massara et al.	2006/0204557 A1	9/2006	Gupta et al.
2005/0025833 A1	2/2005	Aschkenasay et al.	2006/0233743 A1	10/2006	Kelly
2005/0031651 A1	2/2005	Gervais et al.	2006/0233841 A1	10/2006	Pushpala
2005/0042173 A1	2/2005	Besse et al.	2006/0235037 A1	10/2006	Purandare et al.
2005/0042268 A1	2/2005	Aschkenasay et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0048116 A1	3/2005	Straub et al.	2006/0246122 A1	11/2006	Langguth et al.
2005/0054991 A1	3/2005	Paterson	2006/0247216 A1	11/2006	Haj-Yehia
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0247221 A1	11/2006	Coelingh Bennink
2005/0085453 A1	4/2005	Govindarajan	2006/0251581 A1	11/2006	Madenjian
2005/0101579 A1	5/2005	Shippen	2006/0252049 A1	11/2006	Shuler et al.
2005/0113350 A1	5/2005	Duesterberg et al.	2006/0257472 A1	11/2006	Neilsen
2005/0118244 A1	6/2005	Theobld	2006/0275218 A1	12/2006	Besonov
2005/0118272 A1	6/2005	Besse et al.	2006/0292223 A1	12/2006	Nagi et al.
2005/0129756 A1	6/2005	Podhaisky	2007/0004693 A1	1/2007	Mc Ilroy
2005/0152956 A1	7/2005	Dudley	2007/0004694 A1	1/2007	Woolfson et al.
2005/0153946 A1	7/2005	Hirsh et al.	2007/0009559 A1	1/2007	Alosio
2005/0164977 A1	7/2005	Coelingh Bennink	2007/0009594 A1	1/2007	Grubb
2005/0182105 A1	8/2005	Nirschl et al.	2007/0010550 A1	1/2007	McKenzie
2005/0186141 A1	8/2005	Gonda	2007/0014839 A1	1/2007	Bracht
2005/0187267 A1	8/2005	Hamann et al.	2007/0015698 A1	1/2007	Goldstein
2005/0192253 A1	9/2005	Salvati et al.	2007/0021360 A1	1/2007	Nyce et al.
2005/0192310 A1	9/2005	Gavai et al.	2007/0027201 A1	2/2007	McComas et al.
2005/0196434 A1	9/2005	Briere	2007/0031491 A1	2/2007	Levine et al.
2005/0207990 A1	9/2005	Funke et al.	2007/0037780 A1	2/2007	Anigbogu
2005/0209209 A1	9/2005	Koch et al.	2007/0037782 A1	2/2007	Suzuki
2005/0214384 A1	9/2005	Juturu et al.	2007/0042038 A1	2/2007	Besse
2005/0220825 A1	10/2005	Funke et al.	2007/0060589 A1	3/2007	Purandare et al.
2005/0220900 A1	10/2005	Wuttke	2007/0066628 A1	3/2007	Zhang et al.
2005/0222106 A1	10/2005	Bracht	2007/0066637 A1	3/2007	Zhang et al.
2005/0228692 A1	10/2005	Hodgdon	2007/0066675 A1	3/2007	Hubler
2005/0228718 A1	10/2005	Austin	2007/0078091 A1	4/2007	Balog et al.
2005/0239747 A1	10/2005	Yuan	2007/0088029 A1	4/2007	Diffendal et al.
2005/0239758 A1	10/2005	Roby	2007/0093548 A1	4/2007	
2005/0244360 A1	11/2005	Billoni			

US 10,206,932 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2007/0116729 A1	5/2007	Palepu	2009/0004246 A1	1/2009	Woolfson
2007/0116829 A1	5/2007	Prakash et al.	2009/0010968 A1	1/2009	Peyrot
2007/0128263 A1	6/2007	Wall	2009/0011041 A1	1/2009	Musaeva
2007/0154533 A1	7/2007	Dudley	2009/0017120 A1	1/2009	Brisco
2007/0167418 A1	7/2007	Ferguson	2009/0022683 A1	1/2009	Park
2007/0178166 A1	8/2007	Bernstein et al.	2009/0047357 A1	2/2009	Tomohira
2007/0184558 A1	8/2007	Roth et al.	2009/0053294 A1	2/2009	Prendergast
2007/0185068 A1	8/2007	Ferguson	2009/0060982 A1	3/2009	Ron et al.
2007/0190022 A1	8/2007	Chiao	2009/0060997 A1	3/2009	Seitz
2007/0191319 A1	8/2007	Ke et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196415 A1	8/2007	Houston	2009/0074859 A1	3/2009	Patel
2007/0196433 A1	8/2007	Ron et al.	2009/0081206 A1	3/2009	Leibovitz
2007/0207225 A1	9/2007	Squadrito	2009/0081278 A1	3/2009	De Graaff et al.
2007/0225281 A1	9/2007	Zhang et al.	2009/0081303 A1	3/2009	Savoir et al.
2007/0232574 A1	10/2007	Bernard	2009/0092656 A1	4/2009	Klamerus et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0093440 A1	4/2009	Murad
2007/0243229 A1	10/2007	Smith et al.	2009/0098069 A1	4/2009	Vacca
2007/0248658 A1	10/2007	Bracht	2009/0099106 A1	4/2009	Phiasivongsa et al.
2007/0254858 A1	11/2007	Cronk	2009/0099149 A1	4/2009	Kresevic
2007/0255197 A1	11/2007	Wilkins	2009/0130029 A1	5/2009	Tamarkin
2007/0264309 A1	11/2007	Chollet et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0264345 A1	11/2007	Eros et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0264349 A1	11/2007	Lee et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0286819 A1	12/2007	DeVries et al.	2009/0143344 A1	6/2009	Chang
2007/0287688 A1	12/2007	Chan	2009/0164341 A1	6/2009	Sunvold et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0175799 A1	7/2009	Tamarkin
2007/0292359 A1	12/2007	Schuz	2009/0181088 A1	7/2009	Song et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0186081 A1	7/2009	Slot
2007/0292461 A1	12/2007	Danziger	2009/0203658 A1	8/2009	Notelovitz
2007/0292493 A1	12/2007	Briere	2009/0214474 A1	8/2009	Rose
2007/0298089 A1	12/2007	Yoshinaga	2009/0227025 A1	9/2009	Jennings
2008/0026035 A1	1/2008	Chollet et al.	2009/0227550 A1	9/2009	Nichols et al.
2008/0026040 A1	1/2008	Guzman	2009/0232897 A1	9/2009	Mattern
2008/0026062 A1	1/2008	Farr et al.	2009/0258096 A1	9/2009	Sahoo et al.
2008/0038219 A1	2/2008	Carlson	2009/0264395 A1	10/2009	Cohen
2008/0038350 A1	2/2008	Gerecke et al.	2009/0269403 A1	10/2009	Creasy
2008/0039405 A1	2/2008	Joseph	2009/0285772 A1	11/2009	Shaked et al.
2008/0050317 A1	2/2008	Besonov	2009/0285869 A1	11/2009	Phiasivongsa et al.
2008/0051351 A1	2/2008	Ghisalberti	2009/0318558 A1	12/2009	Trimble
2008/0063607 A1	3/2008	Berman	2009/0324714 A1	12/2009	Kim et al.
2008/0069779 A1	3/2008	Schuz	2009/0325916 A1	12/2009	Kresevic
2008/0069791 A1	3/2008	Beissert	2010/0008985 A1	1/2010	Zhang et al.
2008/0085877 A1	4/2008	Bortz	2010/0028360 A1	2/2010	Vermeulen
2008/0095831 A1	4/2008	McGraw	2010/0034838 A1	2/2010	Atwood
2008/0095838 A1	4/2008	Abou Chacra-Vemet	2010/0034880 A1	2/2010	Staniforth
2008/0119537 A1	5/2008	Zhang et al.	2010/0040671 A1	2/2010	Sintov
2008/0125402 A1	5/2008	Dilberti	2010/0048523 A1	2/2010	Ahmed et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0055138 A1	2/2010	Bachman et al.
2008/0138390 A1	6/2008	Grichenko	2010/0074959 A1	3/2010	Jacobs
2008/0139392 A1	6/2008	Yuan	2010/0086501 A1	4/2010	Hansom et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0086599 A1	4/2010	Chang
2008/0153789 A1	6/2008	Dmowski	2010/0092568 A1	4/2010	Huempel et al.
2008/0175814 A1	7/2008	Phiasivongsa et al.	2010/0105071 A1	4/2010	Lerner et al.
2008/0175905 A1	7/2008	B1ksh	2010/0119585 A1	5/2010	Laufer et al.
2008/0175908 A1	7/2008	B1ksh	2010/0129320 A1	5/2010	Hille et al.
2008/0188829 A1	8/2008	Creasy	2010/0136105 A1	6/2010	Laurent-Applegate et al.
2008/0206156 A1	8/2008	Cronk	2010/0137265 A1	6/2010	Coelingh Bennink et al.
2008/0206159 A1	8/2008	Schuz	2010/0137271 A1	6/2010	Fauser et al.
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0143420 A1	6/2010	Theobald
2008/0214512 A1	9/2008	Seitz	2010/0143481 A1	6/2010	D Souza
2008/0220069 A1	9/2008	Allison	2010/0150993 A1	6/2010	Zarif
2008/0226698 A1	9/2008	Beste	2010/0152144 A1	6/2010	Hermsmeyer
2008/0227763 A1	9/2008	Paris	2010/0168228 A1	7/2010	Bose et al.
2008/0234199 A1	9/2008	Katamreddy	2010/0183723 A1	7/2010	Danielsson
2008/0234240 A1	9/2008	Duesterberg	2010/0184736 A1	7/2010	Kulkarni et al.
2008/0255078 A1	10/2008	Katamreddy	2010/0190758 A1	7/2010	Chen
2008/0255089 A1	10/2008	Katamreddy	2010/0204326 A1	8/2010	Dong et al.
2008/0261931 A1	10/2008	Stenlof	2010/0210994 A1	8/2010	Schmidt
2008/0113953 A1	12/2008	DeVries et al.	2010/0221195 A1	9/2010	Liu et al.
2008/0114050 A1	12/2008	Fensome et al.	2010/0227797 A1	9/2010	Hsu
2008/0299220 A1	12/2008	Tamarkin et al.	2010/0240626 A1	9/2010	Murat
2008/0306036 A1	12/2008	Katamreddy	2010/0247482 A1	9/2010	Setiawan
2008/0312197 A1	12/2008	Rodriguez	2010/0247632 A1	9/2010	Leibovitz
2008/0312198 A1	12/2008	Rodriguez	2010/0247635 A1	9/2010	Phiasivongsa et al.
2008/0319078 A1	12/2008	Katamreddy	2010/0255085 A1	10/2010	Savoir et al.

US 10,206,932 B2

Page 8

(56)

References Cited**U.S. PATENT DOCUMENTS**

2010/0291191 A1	11/2010	Lapitsky	2012/0128625 A1	5/2012	Shalwitz et al.
2010/0292199 A1	11/2010	Leverd	2012/0128654 A1	5/2012	Terpstra
2010/0303825 A9	12/2010	Sirbasku	2012/0128683 A1	5/2012	Shantha
2010/0312137 A1	12/2010	Gilmour et al.	2012/0128733 A1	5/2012	Perrin
2010/0316724 A1	12/2010	Whitfield et al.	2012/0128777 A1	5/2012	Keck et al.
2010/0322884 A1	12/2010	Wilkins	2012/0129773 A1	5/2012	Geier
2010/0330168 A1	12/2010	Gicquel et al.	2012/0129819 A1	5/2012	Vancaillie
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0136013 A1	5/2012	Wennogle
2011/0039814 A1	2/2011	Ross	2012/0142645 A1	6/2012	Marx
2011/0053845 A1	3/2011	Levine et al.	2012/0148670 A1	6/2012	Lee
2011/0066473 A1	3/2011	Bernick et al.	2012/0149748 A1	6/2012	Shanler et al.
2011/0076775 A1	3/2011	Stewart et al.	2012/0172343 A1	7/2012	Schuermann
2011/0076776 A1	3/2011	Stewart et al.	2012/0184515 A1	7/2012	Schwede
2011/0086825 A1	4/2011	Chatroux	2012/0231052 A1	9/2012	Brinton
2011/0087192 A1	4/2011	Uhland	2012/0269721 A1	10/2012	Weng et al.
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0269878 A2	10/2012	Cantor et al.
2011/0098258 A1	4/2011	Canet	2012/0277249 A1	11/2012	Tarrand
2011/0098631 A1	4/2011	McIntyre et al.	2012/0277727 A1	11/2012	Doshi
2011/0104268 A1	5/2011	Segot	2012/0283671 A1	11/2012	Shibata et al.
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	2012/0295911 A1	11/2012	Mannion
2011/0130372 A1	6/2011	Marliani	2012/0301517 A1	11/2012	Warner
2011/0135719 A1	6/2011	Besins et al.	2012/0301538 A1	11/2012	Latere
2011/0142945 A1	6/2011	Chen	2012/0302535 A1	11/2012	Caufriez
2011/0152840 A1	6/2011	Lee	2012/0316130 A1	12/2012	Hendrix
2011/0158920 A1	6/2011	Fisher	2012/0316496 A1	12/2012	Horres
2011/0171140 A1	7/2011	Illum	2012/0321579 A1	12/2012	Edelson
2011/0182997 A1	7/2011	Lewis et al.	2012/0322779 A9	12/2012	Voskuhl
2011/0190201 A1	8/2011	Wood, Jr.	2012/0328549 A1	12/2012	Edelson
2011/0195031 A1	8/2011	Du	2012/0329738 A1	12/2012	Liu
2011/0195114 A1	8/2011	Carrara et al.	2013/0004619 A1	1/2013	Goh
2011/0195944 A1	8/2011	Mura et al.	2013/0011342 A1	1/2013	Hazot
2011/0217341 A1	9/2011	Sah	2013/0017239 A1	1/2013	Fernandez
2011/0238003 A1	9/2011	Karabelas	2013/0022674 A1	1/2013	Dudley et al.
2011/0244043 A1	10/2011	Wang	2013/0023505 A1	1/2013	Garfield
2011/0250256 A1	10/2011	Hyun Oh	2013/0023823 A1	1/2013	Volland
2011/0250259 A1	10/2011	Buckman	2013/0028850 A1	1/2013	Hazot
2011/0250274 A1	10/2011	Shaked et al.	2013/0029947 A1	1/2013	Nachaegari et al.
2011/0256092 A1	10/2011	Phiasivongsa et al.	2013/0045266 A1	2/2013	Kang
2011/0262373 A1	10/2011	Umbert Millet	2013/0045953 A1	2/2013	Grenier
2011/0262494 A1	10/2011	Achleitner et al.	2013/0059795 A1	3/2013	Lo
2011/0268665 A1	11/2011	Tamarkin et al.	2013/0064897 A1	3/2013	Binay
2011/0275584 A1	11/2011	Volkmann	2013/0072466 A1	3/2013	Choi
2011/0281832 A1	11/2011	Wennogle	2013/0084257 A1	4/2013	Ishida
2011/0287094 A1	11/2011	Penhasi	2013/0085123 A1	4/2013	Zhao
2011/0293720 A1	12/2011	General et al.	2013/0089574 A1	4/2013	Stock
2011/0294738 A1	12/2011	Kuliopoulos	2013/0090318 A1	4/2013	Gainer
2011/0300167 A1	12/2011	Covic	2013/0102781 A1	4/2013	Ely
2011/0301087 A1	12/2011	McBride	2013/0108551 A1	5/2013	Gruell
2011/0306579 A1	12/2011	Stein	2013/0116215 A1	5/2013	Lleo
2011/0311592 A1	12/2011	Birbara	2013/0116222 A1	5/2013	Altomari
2011/0312927 A1	12/2011	Nachaegari et al.	2013/0122051 A1	5/2013	Gullapalli
2011/0312928 A1	12/2011	Nachaegari et al.	2013/0123175 A1	5/2013	McKee
2011/0318405 A1	12/2011	Erwin	2013/0123220 A1	5/2013	Queiroz
2011/0318431 A1	12/2011	Gulati	2013/0123351 A1	5/2013	Dewitt
2012/0009276 A1	1/2012	De Groot	2013/0129818 A1	5/2013	Bernick et al.
2012/0015350 A1	1/2012	Nabatiyan et al.	2013/0131027 A1	5/2013	Schmitz
2012/0021041 A1	1/2012	Rossi	2013/0131028 A1	5/2013	Snyder
2012/0028888 A1	2/2012	Janz	2013/0131029 A1	5/2013	Baltussen
2012/0028910 A1	2/2012	Takruri	2013/0149314 A1	6/2013	Bullerdiek
2012/0028936 A1	2/2012	Popova	2013/0164225 A1	6/2013	Besonov
2012/0045532 A1	2/2012	Cohen	2013/0164346 A1	6/2013	Son
2012/0046264 A1	2/2012	Lieb	2013/0165744 A1	6/2013	Carson
2012/0046518 A1	2/2012	Yoakum	2013/0178452 A1	7/2013	King
2012/0052077 A1	3/2012	Truitt, III et al.	2013/0183254 A1	7/2013	Cochran
2012/0058171 A1	3/2012	Zeeman	2013/0183325 A1	7/2013	Sforzini
2012/0058962 A1	3/2012	Sparrow	2013/0189193 A1	7/2013	Besonov
2012/0058979 A1	3/2012	Auspitz	2013/0189196 A1	7/2013	Tamarkin
2012/0064135 A1	3/2012	Harms	2013/0189230 A1	7/2013	Van D Kooy
2012/0065179 A1	3/2012	Andersson	2013/0189368 A1	7/2013	Mosqueira
2012/0065221 A1	3/2012	Babul	2013/0210709 A1	8/2013	Covic
2012/0087872 A1	4/2012	Schuz	2013/0216550 A1	8/2013	Penninger
2012/0101073 A1	4/2012	Mannion	2013/0216596 A1	8/2013	Fernandez
2012/0121517 A1	5/2012	Kim	2013/0224177 A1	8/2013	Kim
2012/0121692 A1	5/2012	Fang	2013/0224257 A1	8/2013	Sah
2012/0122829 A1	5/2012	Masini	2013/0224268 A1	8/2013	Jaikaria

US 10,206,932 B2

Page 9

(56)	References Cited		2017/0281646 A1	10/2017	Inskeep et al.
U.S. PATENT DOCUMENTS		2017/0281647 A1	10/2017	Shadiack et al.	
		2017/0281776 A1	10/2017	Shadiack et al.	
					FOREIGN PATENT DOCUMENTS
2013/0224300 A1	8/2013	Maggio	CN	102258455 A	11/2011
2013/0225412 A1	8/2013	Sardari Lodriche	EP	0275716 A1	7/1988
2013/0225542 A1	8/2013	Frick	EP	0279977 A2	8/1988
2013/0226113 A1	8/2013	Langguth	EP	0622075 A1	11/1994
2013/0243696 A1	9/2013	Wang	EP	0785211 A1	7/1997
2013/0245253 A1	9/2013	Mook	EP	0785212 A1	7/1997
2013/0245570 A1	9/2013	Jackson	EP	0811381 A1	12/1997
2013/0261096 A1	10/2013	Merian	EP	0904064 A1	3/1999
2013/0266645 A1	10/2013	Schoenecker	EP	1094781 B1	7/2008
2013/0267485 A1	10/2013	Da Silva Maia Filho	EP	2191833 A1	6/2010
2013/0273167 A1	10/2013	Kim	GB	452238 A	8/1936
2013/0274211 A1	10/2013	Prusthy	GB	720561 A	12/1954
2013/0280213 A1	10/2013	Voskuhl	GB	848881 A	9/1960
2013/0316374 A1	11/2013	Menon	GB	874368 A	8/1961
2013/0317065 A1	11/2013	Seto	GB	1589946 A	5/1981
2013/0317315 A1	11/2013	Tsang	IN	2005KOL00053	8/2005
2013/0324565 A1	12/2013	Zhao	IN	216026	3/2008
2013/0331363 A1	12/2013	Zhao	IN	244217	11/2010
2013/0338122 A1	12/2013	Bernick et al.	JP	H4-503810	9/1990
2013/0338123 A1	12/2013	Bernick et al.	JP	H2-264725 A	10/1990
2013/0338124 A1	12/2013	Zhao	WO	1990011064	10/1990
2013/0345187 A1	12/2013	Rodriguez Oquendo	WO	1993017686	9/1993
2014/0018335 A1	1/2014	Seto	WO	1994022426	10/1994
2014/0024590 A1	1/2014	Taylor	WO	1995030409	11/1995
2014/0031289 A1	1/2014	Kim	WO	1996009826	4/1996
2014/0031323 A1	1/2014	Perez	WO	1996019975	7/1996
2014/0066416 A1	3/2014	Leunis	WO	1996030000	10/1996
2014/0072531 A1	3/2014	Oh	WO	1997005491	2/1997
2014/0079686 A1	3/2014	Prouty	WO	1997043989	11/1997
2014/0088051 A1	3/2014	Bernick et al.	WO	1998010293	3/1998
2014/0088058 A1	3/2014	Maurizio	WO	1998032465	7/1998
2014/0088059 A1	3/2014	Santha	WO	1998051280	11/1998
2014/0094426 A1	4/2014	Drummond	WO	1999022680 A1	5/1999
2014/0094440 A1	4/2014	Bernick et al.	WO	1999032072	7/1999
2014/0094441 A1	4/2014	Bernick et al.	WO	1999039700	8/1999
2014/0099362 A1	4/2014	Bernick et al.	WO	1999042109	8/1999
2014/0100159 A1	4/2014	Conrad	WO	1999043304	9/1999
2014/0100204 A1	4/2014	Bernick et al.	WO	1999048477	9/1999
2014/0100205 A1	4/2014	Bernick et al.	WO	1999053910	10/1999
2014/0100206 A1	4/2014	Cacace	WO	1999062497 A1	12/1999
2014/0113889 A1	4/2014	Haine	WO	1999063974	12/1999
2014/0127185 A1	5/2014	Sayeed	WO	2000001351	1/2000
2014/0127280 A1	5/2014	Jukarainen	WO	2000006175	2/2000
2014/0127308 A1	5/2014	Opara	WO	2000038659	6/2000
2014/0128798 A1	5/2014	Malanchin	WO	2000045795	8/2000
2014/0148491 A1	5/2014	Valia et al.	WO	2000050007	8/2000
2014/0186332 A1	7/2014	Ezrin	WO	2000059577	10/2000
2014/0187487 A1	7/2014	Shoichet	WO	2000076522	12/2000
2014/0193523 A1	7/2014	Henry	WO	2001037808	5/2001
2014/0194396 A1	7/2014	Wennogle	WO	2001054699	8/2001
2014/0206616 A1	7/2014	Ko et al.	WO	2001060325	8/2001
2014/0213565 A1	7/2014	Bernick et al.	WO	2001087276	11/2001
2014/0329783 A1	11/2014	Bernick et al.	WO	2001091757	12/2001
2014/0370084 A1	12/2014	Bernick et al.	WO	2002007700	1/2002
2014/0371182 A1	12/2014	Bernick et al.	WO	2002011768	2/2002
2014/0371183 A1	12/2014	Bernick et al.	WO	2002022132	3/2002
2014/0371184 A1	12/2014	Bernick et al.	WO	2002040008	5/2002
2014/0371185 A1	12/2014	Bernick et al.	WO	2002041878	5/2002
2015/0031654 A1	1/2015	Amadio	WO	2002053131	7/2002
2015/0045335 A1	2/2015	Bernick et al.	WO	2002078602	10/2002
2015/0133421 A1	5/2015	Bernick et al.	WO	2002078604	10/2002
2015/0164789 A1	6/2015	Bernick et al.	WO	2003028667	4/2003
2015/0224117 A1	8/2015	Bernick et al.	WO	2003041718	5/2003
2015/0224118 A1	8/2015	Bernick et al.	WO	2003041741	5/2003
2015/0302435 A1	10/2015	Bernick et al.	WO	2003068186	8/2003
2015/0342963 A1	12/2015	Bernick et al.	WO	2003077923	9/2003
2015/0352126 A1	12/2015	Bernick et al.	WO	2003082254	10/2003
2015/0359737 A1	12/2015	Bernick et al.	WO	2003092588	11/2003
2016/0030449 A1	2/2016	Persicaner et al.	WO	2004014397 A1	2/2004
2016/0213685 A1	7/2016	Bernick et al.	WO	2004014432	2/2004
2017/0056418 A1	3/2017	Thorsteinsson et al.	WO	2004017983	3/2004
2017/0216310 A1	8/2017	Mirkin et al.	WO	2004032897	4/2004
2017/0281645 A1	10/2017	Shadiack et al.	WO	2004052336	6/2004

US 10,206,932 B2

Page 10

(56)	References Cited					
FOREIGN PATENT DOCUMENTS						
WO	2004054540	7/2004	WO	2013144356	A1	10/2013
WO	2004080413	9/2004	WO	2013149258	A2	10/2013
WO	2004110408 A2	12/2004	WO	2013158454	A2	10/2013
WO	2005027911	3/2005	WO	2013170052	A1	11/2013
WO	2005030175	4/2005	WO	2013178587	A1	12/2013
WO	2007076144 A2	7/2005	WO	2013181449	A1	12/2013
WO	2005081825	9/2005	WO	2013192248		12/2013
WO	2005087194	9/2005	WO	2013192249		12/2013
WO	2005087199	9/2005	WO	2013192250		12/2013
WO	2005105059	11/2005	WO	2013192251		12/2013
WO	2005115335	12/2005	WO	2014001904	A1	1/2014
WO	2005120470	12/2005	WO	2014004424	A1	1/2014
WO	2005120517	12/2005	WO	2014009434	A1	1/2014
WO	2006013369	2/2006	WO	2014018569	A1	1/2014
WO	2006034090	3/2006	WO	2014018570	A1	1/2014
WO	2006036899	4/2006	WO	2014018571	A2	1/2014
WO	2006053172	5/2006	WO	2014018856	A1	1/2014
WO	2006105615	10/2006	WO	2014018932	A2	1/2014
WO	2006113505	10/2006	WO	2014031958	A1	2/2014
WO	2006138686	12/2006	WO	2014041120	A1	3/2014
WO	2006138735	12/2006	WO	2014052792	A1	4/2014
WO	2007045027	4/2007	WO	2014056897	A1	4/2014
WO	2007103294	9/2007	WO	2014066442	A2	5/2014
WO	2007120868	10/2007	WO	2014074846	A1	5/2014
WO	2007123790	11/2007	WO	2014076231	A1	5/2014
WO	2007124250	11/2007	WO	2014076569	A2	5/2014
WO	2007144151	12/2007	WO	2014081598	A1	5/2014
WO	2008049516	5/2008	WO	2014086739	A1	6/2014
WO	2008152444	12/2008	WO	2014093114	A1	6/2014
WO	2009002542	12/2008	WO	2014104784	A1	7/2014
WO	2009036311	3/2009	WO	2015179782	A1	11/2015
WO	2009040818	4/2009	WO	2016018993	A1	2/2016
WO	2009069006	6/2009	OTHER PUBLICATIONS			
WO	2009098072	8/2009	U.S. Appl. No. 14/099,545, filed Dec. 6, 2013, U.S. Pat. No. 8,846,648, Sep. 30, 2014.			
WO	2009133352	11/2009	U.S. Appl. No. 14/099,562, filed Dec. 6, 2013, U.S. Pat. No. 8,987,237, Mar. 24, 2015.			
WO	2010033188	3/2010	U.S. Appl. No. 14/099,571, filed Dec. 6, 2013, U.S. Pat. No. 8,846,649, Sep. 30, 2014.			
WO	2010146872	12/2010	U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, U.S. Pat. No. 9,012,434, Apr. 21, 2015.			
WO	2011000210	1/2011	U.S. Appl. No. 14/099,598, filed Dec. 6, 2013, U.S. Pat. No. 8,987,238, Mar. 24, 2015.			
WO	2011073995	6/2011	U.S. Appl. No. 14/099,612, filed Dec. 6, 2013, U.S. Pat. No. 8,933,059, Jan. 13, 2015.			
WO	2011120084	10/2011	U.S. Appl. No. 14/099,623, filed Dec. 6, 2013, U.S. Pat. No. 9,006,222, Apr. 14, 2015.			
WO	2011128336	10/2011	U.S. Appl. No. 14/106,655, filed Dec. 13, 2013.			
WO	2012009778	1/2012	U.S. Appl. No. 14/125,554, filed Jan. 25, 2013, U.S. Pat. No. 9,248,136, Feb. 2, 2016.			
WO	2012024361	2/2012	U.S. Appl. No. 14/136,048, filed Dec. 20, 2013, U.S. Pat. No. 9,180,091, Nov. 10, 2015.			
WO	2012055814 A1	5/2012	U.S. Appl. No. 14/475,814, filed Sep. 3, 2014, U.S. Pat. No. 8,993,548, Mar. 31, 2015.			
WO	2012055840 A1	5/2012	U.S. Appl. No. 14/475,864, filed Sep. 3, 2014, U.S. Pat. No. 8,993,549, Mar. 31, 2015.			
WO	2012065740	5/2012	U.S. Appl. No. 14/475,946, filed Sep. 3, 2014, U.S. Pat. No. 9,114,145, Aug. 25, 2015.			
WO	2012098090 A1	7/2012	U.S. Appl. No. 14/476,040, filed Sep. 3, 2014, U.S. Pat. No. 9,114,146, Aug. 25, 2015.			
WO	2012116277 A1	8/2012	U.S. Appl. No. 14/512,046, filed Oct. 10, 2014.			
WO	2012118563 A2	9/2012	U.S. Appl. No. 14/521,002, filed Oct. 22, 2014.			
WO	2012120365 A1	9/2012	U.S. Appl. No. 14/521,230, filed Oct. 22, 2014.			
WO	2012127501 A2	9/2012	U.S. Appl. No. 14/624,051, filed Feb. 17, 2015, U.S. Pat. No. 9,289,382, Mar. 22, 2016.			
WO	2012156561 A1	11/2012	U.S. Appl. No. 14/649,818, filed Jun. 18, 2013.			
WO	2012156822 A1	11/2012	U.S. Appl. No. 14/690,913, filed Apr. 20, 2015.			
WO	2012158483 A2	11/2012	U.S. Appl. No. 14/690,955, filed Apr. 20, 2015.			
WO	2012166909 A1	12/2012	U.S. Appl. No. 14/812,179, filed Jul. 29, 2015.			
WO	2012170578 A1	12/2012	U.S. Appl. No. 14/830,398, filed Aug. 19, 2015.			
WO	2013011501 A1	1/2013	U.S. Appl. No. 15/090,493, filed Apr. 4, 2016.			
WO	2013025449 A1	2/2013	U.S. Appl. No. 15/372,385, filed Dec. 7, 2016.			
WO	2013028639 A1	2/2013	U.S. Appl. No. 15/420,019, filed Jan. 30, 2017.			
WO	2013035101 A1	3/2013	U.S. Appl. No. 15/475,052, filed Mar. 30, 2017.			
WO	2013044067 A1	3/2013				
WO	2013045404 A2	4/2013				
WO	2013059285 A1	4/2013				
WO	2013063279 A1	5/2013				
WO	2013064620 A1	5/2013				
WO	2013071281 A1	5/2013				
WO	2013078422 A2	5/2013				
WO	2013088254	6/2013				
WO	2013102665 A1	7/2013				
WO	2013106437 A1	7/2013				
WO	2013112947 A1	8/2013				
WO	2013113690	8/2013				
WO	2013124415 A1	8/2013				
WO	2013127727 A1	9/2013				
WO	2013127728 A1	9/2013				

US 10,206,932 B2

Page 11

(56)

References Cited

OTHER PUBLICATIONS

- U.S. Appl. No. 15/475,068, filed Mar. 30, 2017.
- U.S. Appl. No. 15/832,750, filed Dec. 5, 2017.
- U.S. Appl. No. 15/832,757, filed Dec. 5, 2017.
- U.S. Appl. No. 15/893,542, filed Feb. 9, 2018.
- U.S. Appl. No. 15/893,546, filed Feb. 9, 2018.
- U.S. Appl. No. 15/893,550, filed Feb. 9, 2018.
- Abbas et al., Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis, European J of Pharma, 715 (2013) 72-75, Elsevier.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Safty Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Acarturk, Fusun, Mucoadhesive Vaginal Drug Delivery System, Recent Patents on Drug Delivery & Formulation, 2009, vol. 3, pp. 193-195.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, Fountain Journal of Nat. and Appl. Sciences, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, Neuroscience, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceuticals substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Araya-Siblja et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Araya-Siblja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Siblja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Siblja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Araya-Siblja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, Menopause: The Journal of the North American Menopause Society, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, Advances in Therapy®, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, Yale J Biology and Medicine, vol. 35, Feb. 1963, pp. 329-340.
- Azeem, Adnan et al., Microemulsions as a Surrogate Carrier for Dermal Drug Delivery, Drug Development and Industrial Pharmacy, May 2000, vol. 35, No. 5, pp. 525-547 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/03639040802448646>.
- Azure Pharma, Inc., ELESTRINTM—Estradiol Gel, Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, Aug. 2009.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, Current Medicinal Chemistry, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, Biology of Reproduction 52, 1327-1333 (1995).
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani Bhagu R. et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3):756-759.
- Bhavnani et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER α and ER β , Endocrinology, Oct. 2008, 149(10):4857-4870.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductiveaged female subjects, Fertility and Sterility# vol. 94, No. 4, Sep. 2010, Elsevier.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index> [Feb. 3, 2014 1:37:50 PM].
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moleculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Castelo-Branco Camil et al., "Treatment of atrophic vaaginitis," Therapy, 2007, vol. 4, No. 3, pp. 349-353.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- Chamblin et al., Interest of Multifunctional Lipid Excipients: Case of Gelucire® 44/14, Drug Development and Industrial Pharmacy, vol. 31, No. 6, pp. 527-534 (Year: 2005).
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Cho, Y.A. et al., Transdermal Delivery of Ketorolac Tromethamine: Effects of Vehicles and Penetration Enhancers, Drug Development and Industrial Pharmacy, 30(6):557-564, Jun. 2004.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, J Clin Oncol 11:2417-2426, 1993.

US 10,206,932 B2

Page 12

- (56) **References Cited**
- OTHER PUBLICATIONS**
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008; 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance , *Contact Dermatitis*, 71, 264-272, 2014.
- Chun et al., Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles . . . , *J. Kor. Pharm. Sci.*, vol. 35, No. 3, pp. 173-177 (2005).
- Cicinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, March 2000, pp. 403-406.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, *Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div.*, vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Committee Opinion, Incidentally Detected Short Cervical Length, *Committee of Obstetric Practice, Obstetrics & Gynecology, ACOG*, vol. 119, No. 4, Apr. 2012, pp. 879-882.
- Commodari, Fernando, Comparison of 17 β -estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A. et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, *Research Letters*, Apr. 25, 1998.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," *Southern Medical Journal*, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Corn Refiners Association, *Corn Oil*, 5th Edition, Washington, D.C., 2006.
- Crandall, Carolyn, "Vaginal Estrogen Preparations: A Review of Safety and Efficacy for Vaginal Atrophy," *Journal of Women's Health*, 2002, vol. 11, No. 10, pp. 857-877.
- CREMER Care, "MIGLYOL® 810, 812 INCI: Caprylic/Capric Triglyceride," *CREMER OLEO GmbH & Co. KG*, pp. 1-7, available at http://s3.amazonaws.com/petercremerma/products/spec_sheets/159/339/301_originai/MIGL_YOL_81_0_812_TDS.pdf?1389204445 (Mar. 2013) accessed on Dec. 30, 2016.
- Critchley et al., Estrogen Receptor β , But Not Estrogen Receptor α , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE), vol. 14, 2011, IACSIT Press, Singapore.
- Dideberg, O. et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Diramio, Jackie A., Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs, Masters of Science Thesis, University of Georgia, Athens, Georgia, 2002, 131 pages.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of The North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Duax, William L. et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R. et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *SciFinder, Pharmaceutica Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Estradiol, *The Merck Index Online*, Royal Society of Chemistry, <https://www.rsc.org/Merck-Index/monograph/mono1500003758/estradiol?q=unauthorize>.
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Excipients for Pharmaceuticals, *SASOL OLEFINS & SURFACTANTS GMBH*, 2010, 28 pages.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, PiracicabaB1, Braz.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene B1sed on exposure and effect data, *Contact Dermatitis* 1990; 23: 341-345.
- Fotherby, K., Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, *Contraception*, 1996; 54:59-69.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.*(2013), Elsevier.
- Fuchs et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Cutis. Jun.* 2003;71(6):481-8.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.
- Gäfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Ganam-Quintanar et al., Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss, *International Journal of Pharmaceutics*, vo. 147, No. 2, Feb. 28, 1997, pp. 165-171 (abstract only).
- Garad S. et al., "Preclinical Development for Suspensions," A.K. Kulshreshtha et al. (eds.), *Pharmaceutical Suspensions: From Formulation Development to Manufacturing*, Springer, New York 2010, pp. 127-176.
- Gatfossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gatfossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gatfossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gatfossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/Block-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.

US 10,206,932 B2

Page 13

(56)

References Cited**OTHER PUBLICATIONS**

- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas*, 19 (1994) 103-115.
- Giron-Forest, D. et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Giron-Forest, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Glaser et al, Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al, Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Gunstone, Frank D. et al., *Vegetable Oils in Food Technology: Composition, Properties and Uses*, Blackwell Publishing, CRC Press, 2002.
- Gurney, E.P. et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J.Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- Haner, Barbara, Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hargrove et al., Menopausal Hormone Replacement Therapy with Continuous Daily Oral Micronize Estradiol and Progesterone, *Obstet Gynecol*, vol. 73, No. 4, Apr. 1989, pp. 606-612.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helbling, Ignacio M. et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res.* vol. 31 pp. 795-808, 2014, Springer Science.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Sturdy of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Herman, Aima et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, pp. 1-13.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Holm et al., "Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides," *European Journal of Pharmaceutical Sciences* 20 (2003) 91-97.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hostynk, JJ, Predicting absorption of fragrance chemicals through human skin, *j. Soc.C osmeCt. hem.*, 4 6, 221-229 (Jul./Aug. 1995).
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Humberstone, Andrew et al., "Lipid-based vehicles for the oral delivery of poorly water soluble drugs," *Advanced Drug Delivery Reviews*, 25 (1997) 103-128.
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, *Journal of Cerebral Blood Flow and Metabolism* 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 α -Ethinyl Estradiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 β -Estradiol, *JPET* 290(2):740-747, 1999.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johanson, Gunnar, Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester, *Critical Reviews in Toxicology*, 2000, vol. 30, No. 3, pp. 307-345 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/10408440091159220>.
- Johnson, William S. et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, *J Reprod Fert* (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, *Environmental Health Perspectives* • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karande, et al. Enhancement of transdermal drug delivery via synergistic action of chemicals, *Biochimica et Biophysica Acta*, 1788:2362-2373, Sep. 2009.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, *Contact Dermatitis*, 1992: 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, *Ann. Occup. Hyg.*, vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Kincl et al., Increasing Oral Bioavailability of Progesterone by Formulation, *Journal of Steroid Biochemistry*, 1978, vol. 9, pp. 83-84.
- Knuth et al., Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations, *Advanced Drug Delivery Reviews*, vol. 11, No. 1-2, Jul.-Aug. 1993, pp. 137-167 (abstract only).
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.

US 10,206,932 B2

Page 14

- (56) **References Cited**
- OTHER PUBLICATIONS**
- Komm et al., B1zedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyan, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier (abstract only).
- Kuhnert-Brandstaetter and Grimm. Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II, *Mikrochimica Acta*, vol. 1, pp. 127-139, 1968.
- Kuhnert-Brandstaetter and Junger and Kofler. Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Kuhnert-Brandstaetter and Kofler. Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, *Mikrochimica Acta*, vol. 6, pp. 847-853, 1959.
- Kuhnert-Brandstaetter and Linder. Zur Hydratbildung bei Steroidhormonen, *Sci. Pharm.*, vol. 41(2), pp. 109-116, 1973.
- Kumasaka et al., Effects of Various Forms of Progestin on the the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2). 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol*. Jul. 2011 ; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVV in OBGYN*, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol*. May 2010 ; 202(5): 455.e1-455.e9.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr, The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Lane, Majella E, "Skin penetration enhancers," *International Journal of Pharmaceutics* 447 (2013) 12-21.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G, et al., Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women, *Maturitas, The European Menopause Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17 α - and 17 β -estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lindmark, Tuulikki et al., "Absorption Enhancement through Intracellular Regulation of Tight Junction Permeability by Medium Chain Fatty Acids in Caco-2 Cells," *JPET* 284(1):362-369, 1998.
- Lindmark, Tuulikki et al., "Mechanisms of Absorption Enhancement by Medium Chain Fatty Acids in Intestinal Epithelial Caco-2 Cell Monolayers," *JPET* 275(2):958-964, 1995.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lopes, Luciana B, et al., Enhancement of transdermal delivery of progesterone using medium-chain mono and diglycerides as skin penetration enhancers, *Pharmaceutical Development and Technology*, 14:5, 524-529, Mar. 2009.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Lucy et al., Gonadotropin-releasing hormone at estrus: lutenizing hormone, estradiol, and progesterone during . . . *Biol Reprod* Sep. 1986;35(2):300-311 (abstract only).
- Lvova, M. SH., et al. Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Mac Bride, Maire B, et al., "Vulvovaginal Atrophy," *Mayo Clin Proc*, Jan. 2010, 85(1):87-94.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Magness, R.R., et al., Estrone, Estradiol-17 β and Progesterone Concentrations in Uterine Lymph and Systematic Blood throughout the Porcine Estrone Estrous Cycle, *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- Manson, JoAnn E, et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- McGuffey, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration bv'Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Monti, D. et al., Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin, *International Journal of Pharmaceutics*, 237:209-24, 2002.
- Mueck, A.O. et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol.Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Ng, Jo-Han et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*,35(9) pp. 1035, 2009.

US 10,206,932 B2

Page 15

(56)

References Cited

OTHER PUBLICATIONS

- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- NuGen, What is NuGen HP Hair Growth System.
- NuGest900, NuGest 900™.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical application of pregersterone cream to pre-and post-menopausal women, *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Opinion on the Diethylene Glycol Momoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Panay et al., The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy, *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Panchangnula et al., Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol . . . , *J Pharm Pharmacol.* Sep. 1991;43(9):609-614 (abstract only).
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res.* vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Patel et al., Transdermal Drug Delivery System: A Review, www.thepharmajournal.com, vol. 1, No. 4, 2012, pp. 78-87.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisia L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Position Statement, Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society (NAMS), *Menopause*, vol. 20, No. 9, pp. 888-902.
- Potluri, Praveen and Guru V. Betageri, "Mixed-micellar proliposomal systems for enhanced oral delivery of progesterone," *Drug Delivery*, 2006, vol. 13, No. 3, pp. 227-232.
- Practice Bulletin No. 141, Management of Menopausal Symptoms, *Obstetrics & Gynecology*, ACOG, vol. 123, No. 1, Jan. 2014, pp. 202-216.
- Prajapati Hetal N. et al., "A Comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water Phase Diagram, Solubility Determination and Dispersion Testing for Application in Pharmaceutical Dosage Form Development," *Pharm. Res.* Jan. 2012; 29(1): 285-305. Published online Aug. 23, 2011. doi: 10.1007/s11095-011-0541-3.
- Prajapati Hetal N. et al., "Effect of Difference in Fatty Acid Chain Lengths of Medium-Chain Lipids on Lipid/Surfactant/Water Phase Diagrams and Drug Solubility," *J. Excipients and Food Chem.* 2 (3) 2011:73-88.
- Prajapati, Hetal N. et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol.* Nov. 2008 ; 26(11): 1261-1268.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Product Information Sheet, Body B1llance Cream, Tahitian Noni International, 2013, 1 page.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Progesterone, The Merck Index Online, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index-monograph/print/mono/1500007889/progesterone?q=authorize>.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%202010%202012%20Patches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause a Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014, 6: 139-143.
- Rao, R. et al., "The Affect of Capmul, Labrafil and Transcutol on Progesterone 100 Mg Soft Capsules Bioavailability in Indian Healthy Adult Postmenopausal Female Subjects Under Fasting Conditions," *Bioequivalence & Bioavailability*, 7(2):095-107, 2015.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181, 512-520 (2014).
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *AnnJ Obstet Gynecol*, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010:5 943-954, Dove Press.
- Sallee, Verney L. et al., "Determinants of intestinal mucosal uptake of short- and medium-chain fatty acids and alcohols," *Journal of Lipid Research*, 1973, vol. 14, 475-484.

US 10,206,932 B2

Page 16

(56)

References Cited**OTHER PUBLICATIONS**

- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Salole, Eugene G., The physicochemical properties of oestradiol, Journal of Pharmaceutical & Biomedical Analysis, vol. 5, No. 7, pp. 635-648, 1987.
- Santen, R.J., Menopausal hormone therapy and breast cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, CLIMACTERIC 2014;17:1-14.
- Sarkar, BISU, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ B1se . . . , J Steroids Horm Sci, 4:2, 2013.
- Sarpal, K. et al., "Self emulsifying drug delivery systems: a strategy to improve oral bioavailability," Current Research & Information on Pharmaceuticals Sciences (CRIPS), 2010, vol. 11, No. 3, pp. 42-49.
- Sarrel, et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, American Journal of Public Health, Research and Practice, e1-e6. Published online ahead of print Jul. 18, 2013.
- Satyaranayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, Asian J. Chem., vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), J. Steroid Biochem.Mol. Biol. (2013), Elsevier.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, Maturitas 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, Fertil. Steril. Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, Toxicologic Pathology, 42: 1188-1196, 2014.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Search Report, Extended European Search Report for EP13741053. 6, dated Jul. 1, 2015.
- Search Report, Extended European Search Report for EP13807188. 1, dated Nov. 23, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US12/66406, dated Jan. 24, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/23309, dated Apr. 9, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46442, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46443, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46444, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46445, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US14/61811, dated Jan. 21, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/23041, dated Jun. 30, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/42621, dated Oct. 29, 2015.
- Serantoni, Foresti, et al., 4-Pregn-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, Journal of Experimental & Clinical Cancer Research 2014, 33(1):41, 11 pages.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
- Shufelt et al., Hormone therapy dose, formulation, route delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014, pp. 1-7, 2013.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, Pharmaceutical Technology, Aug. 2014, pp. 28, 30-31.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaproducts.com/catalog/product/sigma/p7556>.
- Simon et al., Effective Treatment of Vaginal atrophy with an Ultra-low-dose estradiol vaginal tablet, Obstetrics & Gynecology, vol. 112, No. 5, Nov. 2008, pp. 1053-1060.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? Menopause: The Journal of the North American Menopause Society, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware et al., Progestogens in hormonal replacement therapy: new molecules, risks, and benefits, Menopause: The Journal of the North American Menopause Society. vol. 9, No. 1, pp. 6-15, 2002.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," Maturitas 47 (2004) 277-283.
- Sitruk-Ware, Regine, Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review, Contraception, Oct. 1987, vol. 36, No. 4, pp. 373-402.
- Smith et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, JAMA Internal Medicine, Published online Sep. 30, 2013, E1-E7. jamanetwork.com.
- Smyth et al., Summary of Toxicological Data, A 2-yr Study of Diethylene Glycol Monoethyl Ether in Rats, Fd Cosmet. Toxicol. vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Thereapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, Contraception, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," Menopause: The Journal of the North American Menopause Society, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z. et al., Ethinyl estradiol and 17 β -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, Contraception 87 (Jun. 2013) vol. 87, No. 6, pp. 706-727.
- Stanczyk, F.Z., "All progestins are not created equal," Steroids 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" Climacteric 2014;17 (Suppl 2):8-11.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," Int J Pharmaceutical Compounding, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Strickley, Robert T., Solubilizing excipients in oral and injectable formulations, Pharmaceutical Research Feb. 2004, vol. 21, Issue 2, pp. 201-230 (abstract only).
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.

US 10,206,932 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Sullivan et al., "A review of the nonclinical safety of Transcitol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, Alternative Medicine Review vol. 12, No. 3, 2007, pp. 259-264.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helveticae, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, Biology of Reproduction 31, 399-413 (1984).
- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, Gynecol Endocrinol, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Int'l. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Thomas, Peter, Characteristics of membrane progestin receptor alpha (mPR α) and progesterone membrane receptor component 1 (PGMRC1) and their roles in mediating rapid progestin actions, Frontiers in Neuroendocrinology 29 (2008) 292-312.
- Tripathi, R. et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PhamSciTech, vol. 11, No. 3, Sep. 2010.
- Trommer et al., Overcoming the stratum Corneum: The modulation of Skin Penetration, Skin Pharmacol Physiol 2006;19:106-121.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- Ueda et al., Topical and Transdermal Drug Products, Pharmacopeial Forum, vol. 35(3) [May-Jun. 2009], 750-754.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- U.S. Appl. No. 13/843,428, filed Jul. 2, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/106,655, filed Jun. 19, 2015 Final Office Action.
- U.S. Appl. No. 13/684,002, filed Mar. 20, 2013_Non-Final_OfficAction.
- U.S. Appl. No. 13/684,002, filed Jul. 16, 2013_Final_OfficAction.
- U.S. Appl. No. 13/684,002, filed Dec. 6, 2013_Notic_of Allowance.
- U.S. Appl. No. 13/843,362, filed Mar. 16, 2015_Restriction_Requirement.
- U.S. Appl. No. 13/843,428, filed Apr. 14, 2015_Restriction_Requirement.
- U.S. Appl. No. 14/099,545, filed Feb. 18, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,545, filed Jul. 14, 2014_Notice_of Allowance.
- U.S. Appl. No. 14/099,562, filed Feb. 20, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,562, filed Mar. 27, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,562, filed Jul. 2, 2014_Final_OfficAction.
- U.S. Appl. No. 14/099,562, filed Dec. 10, 2014_Notice_of Allowance.
- U.S. Appl. No. 14/099,571, filed Mar. 28, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,571, filed Jul. 15, 2014_Notice_of Allowance.
- U.S. Appl. No. 14/099,582, filed Apr. 29, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,582, filed Jun. 17, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,582, filed Nov. 7, 2014_Notice_of Allowance.
- U.S. Appl. No. 14/099,582, filed Jan. 22, 2015_Notice_of Allowance.
- U.S. Appl. No. 14/099,598, filed May 13, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,598, filed Jul. 3, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,598, filed Dec. 10, 2014_Notice_of Allowance.
- U.S. Appl. No. 14/099,612, filed Mar. 20, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,612, filed Oct. 30, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,612, filed Nov. 26, 2014_Notice_of Allowance.
- U.S. Appl. No. 14/099,623, filed Mar. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,623, filed Jul. 18, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,623, filed Dec. 15, 2014_Notice_of Allowance.
- U.S. Appl. No. 14/106,655, filed Jul. 3, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/106,655, filed Dec. 8, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/125,554, filed Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/125,554, filed Apr. 14, 2015_Non-Final_OfficAction.
- U.S. Appl. No. 14/136,048, filed Nov. 4, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/136,048, filed Mar. 12, 2015_Non-Final_OfficAction.
- U.S. Appl. No. 14/475,814, filed Oct. 1, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/475,814, filed Feb. 13, 2015_Notice_of Allowance.
- U.S. Appl. No. 14/475,864, filed Oct. 2, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/475,864, filed Feb. 11, 2015_Notice_of Allowance.
- U.S. Appl. No. 14/476,040, filed Mar. 26, 2015_Restriction_Requirement.
- U.S. Appl. No. 14/521,230, filed Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/521,230, filed Feb. 18, 2015_Non-Final_OfficAction.
- U.S. Appl. No. 14/624,051, filed Apr. 7, 2015_Non-Final_OfficAction.

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(56)

References Cited

OTHER PUBLICATIONS

- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens, *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.
- Voegtlle et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.
- Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.
- Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role For the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).
- Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforb.es/1LIUm1V>, on Feb. 23, 2015, 3 pages.
- Whitehead et al., Absorption and metabolism of oral progesterone, *The British Medical Journal*, vol. 280, No. 6217 (Mar. 22, 1980), pp. 825-827, BMJ Publishing Group.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Wood et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, *Breast Cancer Res Treat* (2007) 101:125-134.
- Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
- Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, *Handbook of Acqueous Solubility Data, Solutions*, 2003, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.
- Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid.

* cited by examiner

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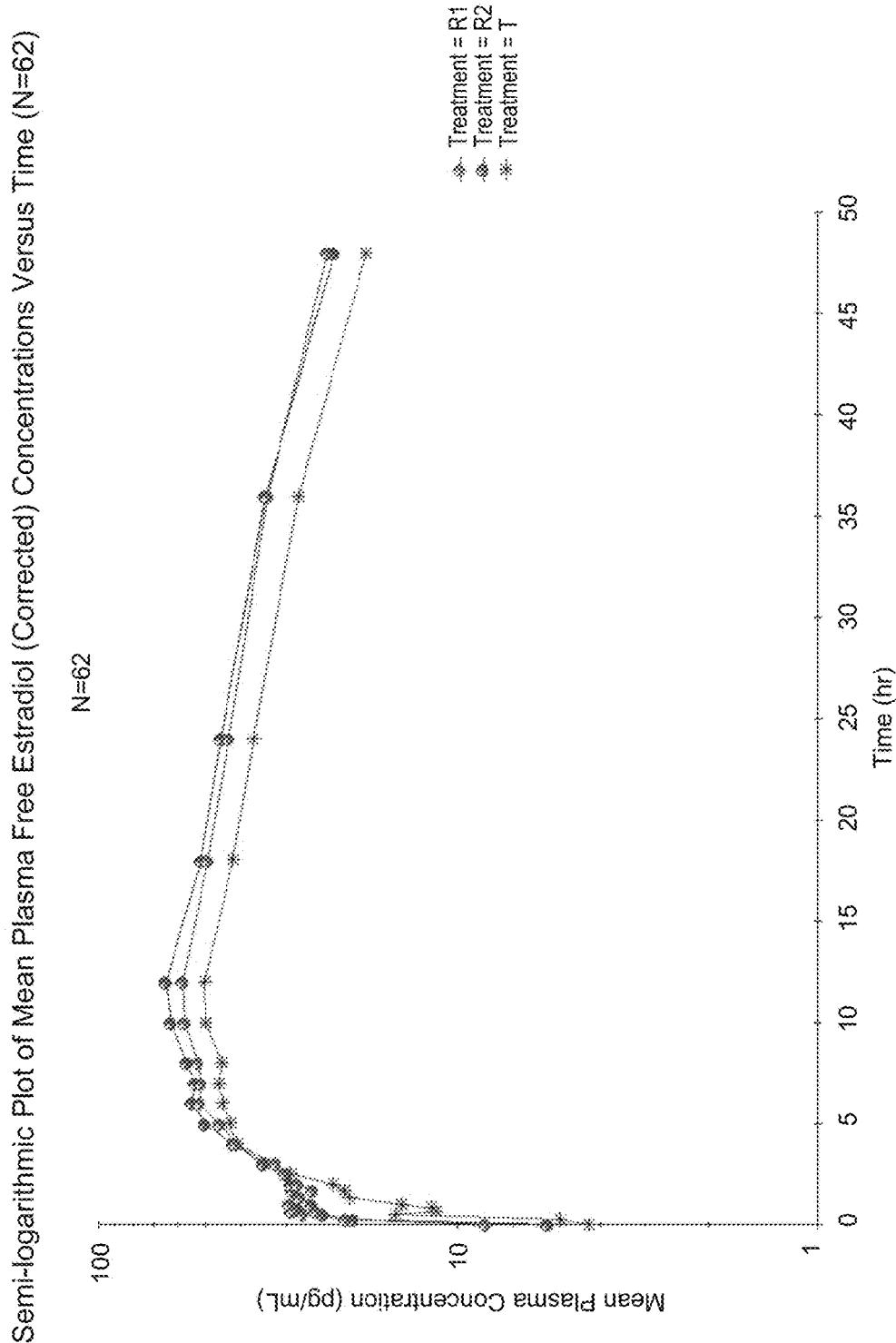


FIG. 1

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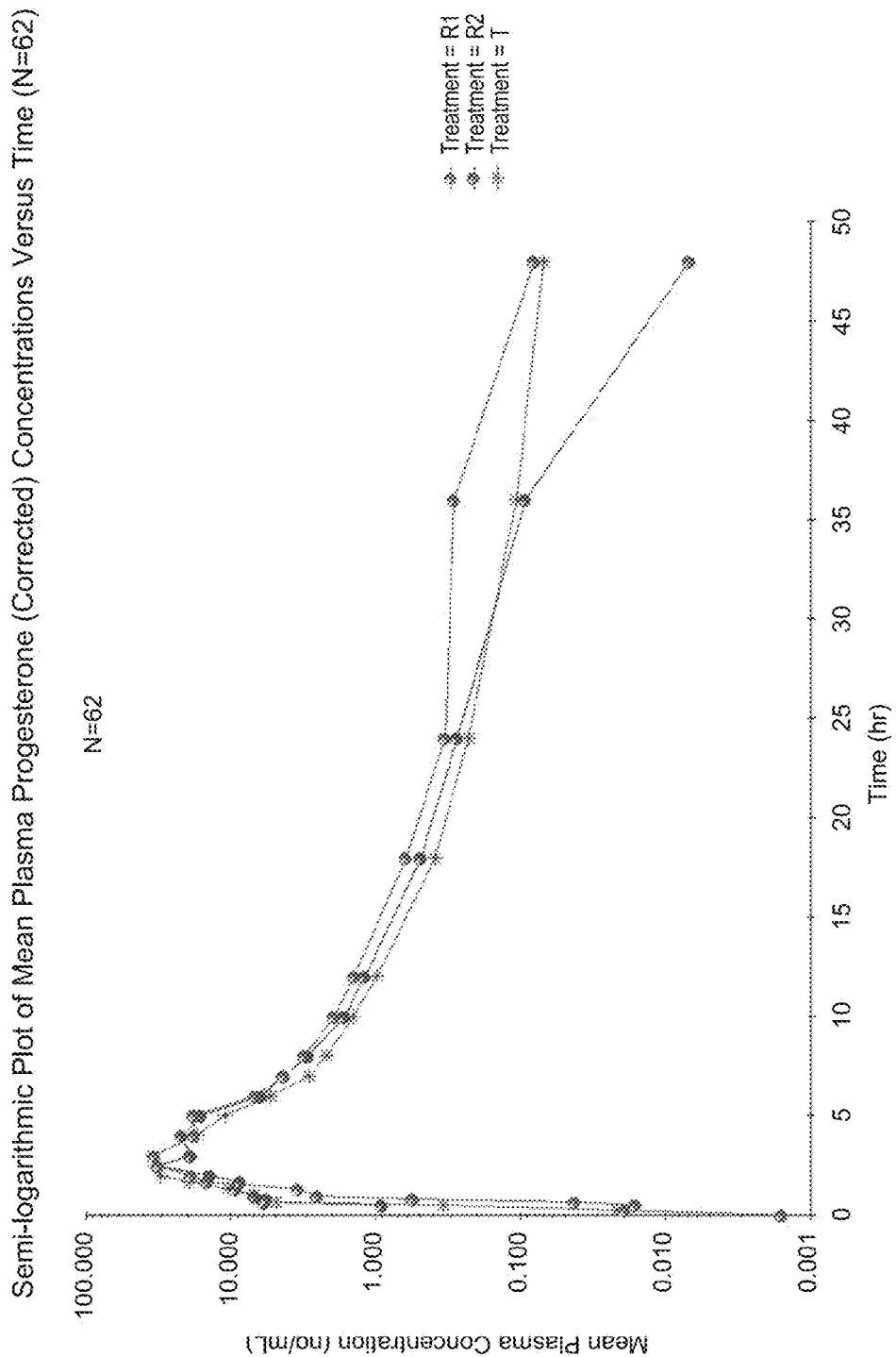


FIG. 2

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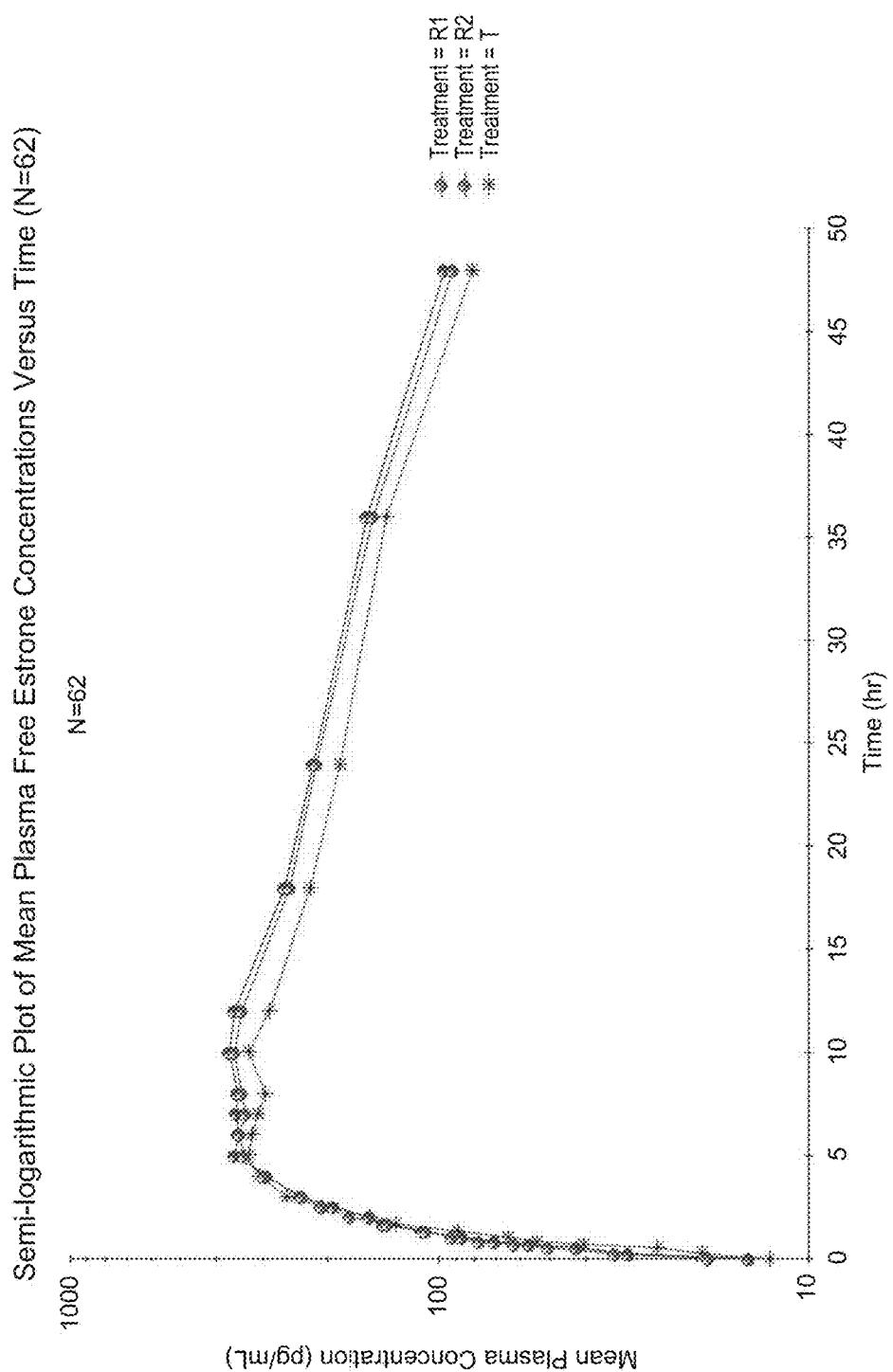


FIG. 3

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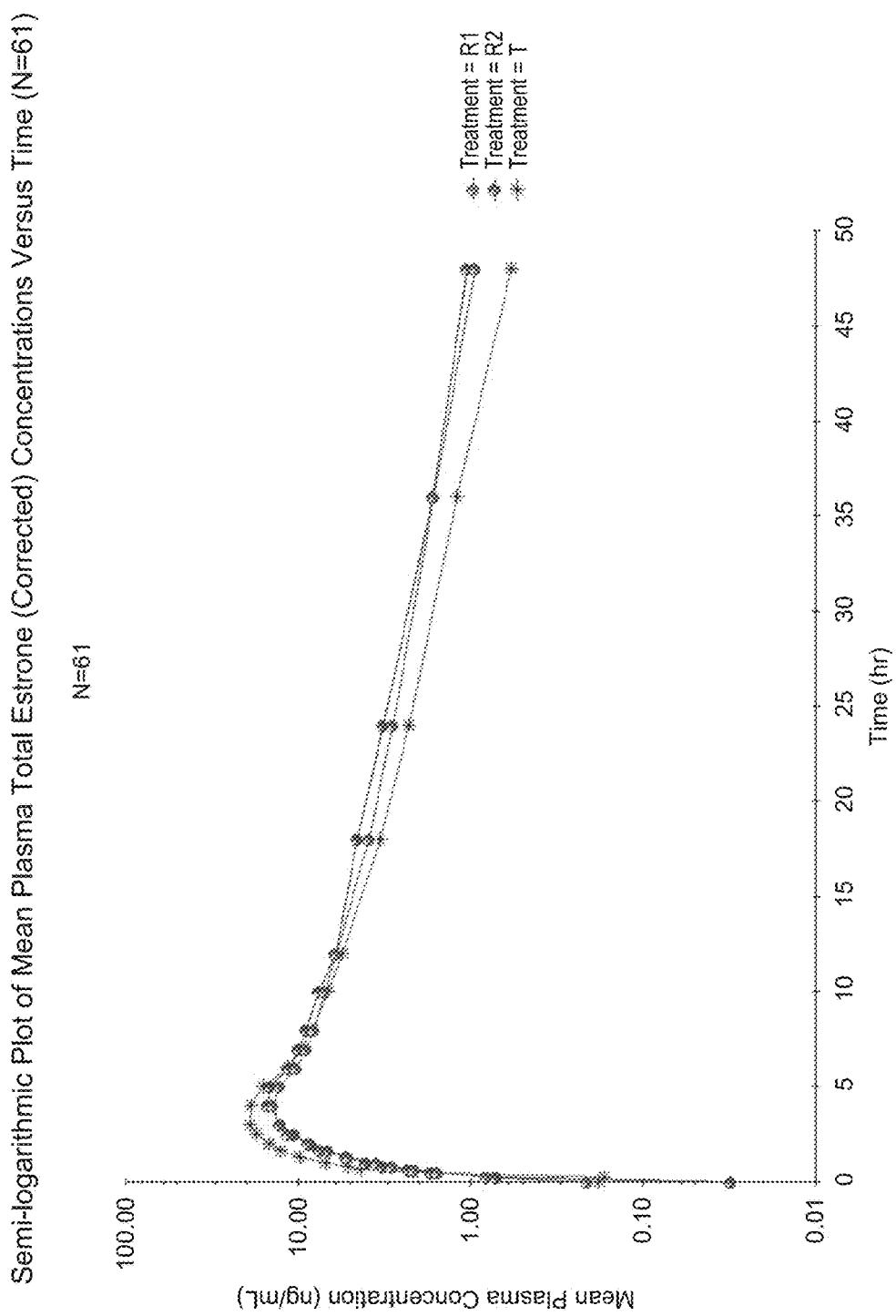


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application claims priority to U.S. Provisional Application Ser. No. 62/002,090, filed May 22, 2014, the content of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

This application relates to pharmaceutical compositions and methods for hormone replacement therapy.

BACKGROUND OF THE INVENTION

Hormone Replacement Therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones in a pre-menopausal, peri-menopausal, menopausal or post-menopausal subject.

BRIEF SUMMARY OF THE INVENTION

In one aspect, pharmaceutical compositions for co-administering estradiol and progesterone to a subject in need of natural hormone replacement therapies are provided. In some embodiments, the pharmaceutical composition comprises: solubilized estradiol, suspended progesterone, and a solubilizing agent, wherein the solubilizing agent is a medium chain (C6-C12) oil and wherein the pharmaceutical composition, when administered to a subject, produces in a plasma sample from the subject one or more pharmacokinetic parameters as described herein (e.g., an area under the curve (AUC)_(0-t) or a C_{max} for estradiol, progesterone, estrone, or total estrone as described herein, e.g., in Tables 18-21).

In some embodiments, the pharmaceutical composition comprises a solubilizing agent that comprises a glyceride of at least one C6-C12 fatty acid. In some embodiments, the glyceride ester is a mixture of mono- and diglycerides (e.g., glyceryl caprylate/caprate). In some embodiments, the fatty acid is predominantly a C8 to C10 fatty acid. In some embodiments, the pharmaceutical composition further comprises a surfactant (e.g., lauroyl polyoxyglyceride). In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.25 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 1 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments,

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ments, the pharmaceutical composition comprises estradiol at a dosage of about 2 mg and comprises progesterone at a dosage of about 200 mg.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve (AUC)_(0-t) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an AUC_(0-t) for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an AUC_(0-t) for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; and a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an AUC_(0-t) for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an AUC_(0-t) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- (ii) one or both of (a) an AUC_(0-t) for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an AUC_(0-t) for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- (iv) one or both of (a) an AUC_(0-t) for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an AUC_(0-t) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an AUC_(0-t) for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an AUC_(0-t)

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for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max}

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C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally

- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 1 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml, and a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, and a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition has the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, the pharmaceutical composition has the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, the pharmaceutical composition has the blood plasma estrone concentration profile of FIG. 3. In some embodiments, the pharmaceutical composition has the blood plasma total estrone concentration profile of FIG. 4.

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In some embodiments, the one or more parameters as described herein (e.g., the $AUC_{(0-t)}$ or C_{max} for progesterone, estradiol, estrone, or total estrone) are measured at regular intervals (e.g., about every 30 minutes, about every 60 minutes, or about every 90 minutes) or at irregular intervals over a period of time such as 24 hours or 48 hours. In some embodiments, the one or more parameters as described herein (e.g., the $AUC_{(0-t)}$ or C_{max} for progesterone, estradiol, estrone, or total estrone) are measured at about 0.25 hr, 0.5 hr, 0.67 hr, 0.83 hr, 1 hr, 1.33 hr, 1.67 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, or 48 hr after administering the pharmaceutical composition to the subject. In some embodiments, the one or more parameters as described herein are measured at regular or irregular intervals following the administration of a single dose or of a first dose of the pharmaceutical composition to the subject.

In another aspect, methods of treating a subject are provided. In some embodiments, the subject has a condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause, such as vasomotor symptoms). In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil as described herein, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein. In some embodiments, the method comprises administering a pharmaceutical composition comprising estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprising progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the method comprises administering a pharmaceutical composition comprising: estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg; estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg; or estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In still another aspect, pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil, wherein the treatment produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein (e.g., an $AUC_{(0-t)}$ or C_{max} for estradiol, progesterone, estrone, or total estrone as described herein, e.g., as described in any of Tables 18-21). In some embodiments, the pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency comprise estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprise progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 18 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 19 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 20 following administration of a

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single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 21 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estradiol.

FIG. 2 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for progesterone.

FIG. 3 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estrone.

FIG. 4 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for total estrone.

DETAILED DESCRIPTION OF THE INVENTION

In the following detailed description of embodiments of this disclosure, reference is made to the accompanying drawings in which like references indicate similar elements, and in which is shown, by way of illustration, specific embodiments in which this disclosure may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice this disclosure, and it is to be understood that other embodiments may be utilized and that other changes may be made without departing from the scope of this disclosure. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of this disclosure is defined only by the appended claims. As used in this disclosure, the term “or” shall be understood to be defined as a logical disjunction (i.e., and/or) and shall not indicate an exclusive disjunction unless expressly indicated as such with the term “either,” “unless,” “alternatively,” and words of similar effect.

I. DEFINITIONS

The term “area under the curve” (“AUC”) refers to the area under the curve defined by changes in the blood, plasma, or serum concentration of an active pharmaceutical ingredient (e.g., estradiol or progesterone), or one or more metabolites of the active pharmaceutical ingredient, over time following the administration of a dose of the active pharmaceutical ingredient. “ $AUC_{0-\infty}$ ” is the area under the concentration-time curve extrapolated to infinity following the administration of a dose. “ AUC_{0-t} ” is the area under the concentration-time curve from time zero to time t following the administration of a dose, wherein t is the last time point with measurable concentration.

The term “ C_{max} ” refers to the maximum value of blood, plasma, or serum concentration shown on the curve that represents changes in blood, plasma, or serum concentrations of an active pharmaceutical ingredient (e.g., progesterone or estradiol), or one or more metabolites of the active pharmaceutical ingredient, over time.

The term “ T_{max} ” refers to the time that it takes for the blood, plasma, or serum concentration of an active pharma-

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ceutical ingredient (e.g., estradiol or progesterone), or of one or more metabolites of the active pharmaceutical ingredient, to reach the maximum value.

Collectively, AUC, C_{max} , and, optionally, T_{max} are the principal pharmacokinetic parameters that can characterize the pharmacokinetic response of a particular drug product, such as progesterone or estradiol, in an animal, especially a mammal, including human, subject.

An “active pharmaceutical ingredient” (API), as used herein, means the active compound or compounds used in formulating a drug product. APIs are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “bioavailability” has the meaning as defined in 21 C.F.R. § 320.1(a): the rate and extent to which an API or active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the API or active ingredient or active moiety becomes available at the site of action. For example, bioavailability can be measured as the amount of API in the blood (whole blood, serum, or plasma) as a function of time. In embodiments, the amount of API is measured in blood plasma. Pharmacokinetic (PK) parameters such as AUC, C_{max} , or T_{max} may be used to measure and assess bioavailability.

The term “bioequivalent” has the meaning as defined in 21 C.F.R. § 320.1(e): the absence of a significant difference in the rate and extent to which the API or active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms or modified release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. In practice, two products are considered bioequivalent if the 90% confidence interval of the AUC, C_{max} , or optionally T_{max} is within 80.00% to 125.00%.

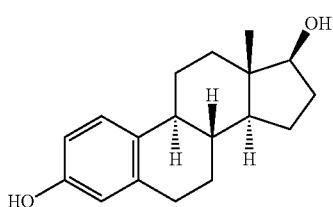
The term “bio-identical hormone” or “body-identical hormone” refers to an active pharmaceutical ingredient that is structurally identical to a hormone naturally or endogenously found in the human body (e.g., estradiol and progesterone).

The term “estrogen” refers to a group of several female sex hormones produced primarily by the ovaries, including estradiol, estrone, and estriol. As used herein, unless otherwise specified, estrogen refers to estradiol.

The term “estradiol” refers to (17 β)-estr-1,3,5(10)-triene-3,17-diol. Estradiol is also interchangeably called 17 β -estradiol, oestradiol, or E2, and is found endogenously in the human body. As used herein, estradiol refers to the bio-identical or body-identical form of estradiol found in the human body having the structure:

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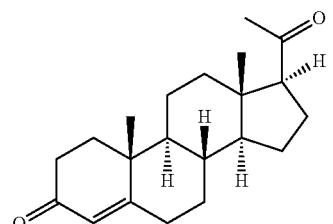
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As used herein, unless specified, estradiol includes estradiol in anhydrous or hemi-hydrate forms. For the purposes of this disclosure, the anhydrous form or the hemihydrate form can be substituted for the other by accounting for the water or lack of water according to well-known and understood techniques.

The term “solubilized estradiol” means that the estradiol or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. Solubilized estradiol may include estradiol that is about 80% solubilized, about 85% solubilized, about 90% solubilized, about 95% solubilized, about 96% solubilized, about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. In some embodiments, the estradiol is “fully solubilized” with all or substantially all of the estradiol being solubilized or dissolved in the solubilizing agent. Fully solubilized estradiol may include estradiol that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The term “progesterone” refers to pregn-4-ene-3,20-dione. Progesterone is also interchangeably called P4 and is found endogenously in the human body. As used herein, progesterone refers to the bio-identical or body-identical form of progesterone found in the human body having the structure:



The term “solubilized progesterone” means that the progesterone or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. In some embodiments, the progesterone is “partially solubilized” with a portion of the progesterone being solubilized or dissolved in the solubilizing agent and a portion of the progesterone being suspended in the solubilizing agent. Partially solubilized progesterone may include progesterone that is about 1% solubilized, about 5% solubilized, about 10% solubilized, about 15% solubilized, about 20% solubilized, about 30% solubilized, about 40% solubilized, about 50% solubilized, about 60% solubilized, about 70% solubilized, about 80% solubilized, about 85% solubilized, about 90% solubilized or about 95% solubilized. In other embodiments, the progesterone is “fully solubilized” with all or substantially all of the progesterone being solubilized or dissolved in the solubilizing agent. Fully solubilized progesterone may include progesterone

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that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

- 5 The terms “micronized progesterone” and “micronized estradiol,” as used herein, include micronized progesterone and micronized estradiol, respectively, having an X50 particle size value below about 15 microns or having an X90 particle size value below about 25 microns. The term “X50”
- 10 means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly,
- 15 the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “solubilizing agent” refers to an agent or combination of agents that solubilize an active pharmaceutical ingredient (e.g., estradiol or progesterone). For example and without limitation, suitable solubilizing agents include medium chain oils and other solvents and co-solvents that solubilize or dissolve an active pharmaceutical ingredient to a desirable extent. Solubilizing agents suitable for use in the formulations disclosed herein are pharmaceutical grade medium chain solubilizing agents (e.g., pharmaceutical grade medium chain oils). It will be understood by those of skill in the art that other excipients or components can be added to or mixed with the solubilizing agent to enhance the properties or performance of the solubilizing agent or resulting formulation. Examples of such excipients include, but are not limited to, surfactants, emulsifiers, thickeners, colorants, flavoring agents, etc. In some embodiments, the solubilizing agent is a medium chain oil and, in some other embodiments, the medium chain oil is combined with a co-solvent(s) or other excipient(s).

The term “medium chain” is used to describe the aliphatic chain length of fatty acid containing molecules. “Medium chain” specifically refers to fatty acids, fatty acid esters, or fatty acid derivatives that contain fatty acid aliphatic tails or carbon chains that contain between 6 (C6) and 14 (C14) carbon atoms.

The terms “medium chain fatty acid” and “medium chain fatty acid derivative” are used to describe fatty acids or fatty acid derivatives with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. Fatty acids consist of an unbranched aliphatic tail attached to a carboxylic acid functional group. Fatty acid derivatives include, for example, fatty acid esters and fatty acid containing molecules, including, without limitation, mono-, di- and triglycerides that include components derived from fatty acids as well as fatty acid esters of ethylene or propylene glycol. Those of skill will appreciate that the aliphatic tails can be saturated or unsaturated (one or more double bonds between carbon atoms). In some embodiments, the aliphatic tails are saturated (i.e., no double bonds between carbon atoms). Medium chain fatty acids or medium chain fatty acid derivatives include those with aliphatic tails having 6-14 carbons, including those that are C6-C14, C6-C12, C8-C14, C8-C12, C6-C10, C8-C10, or others. In embodiments, medium chain fatty acids or medium chain fatty acid derivatives are those that are saturated. Examples include, without limitation, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, and derivatives thereof.

The term “oil,” as used herein, refers to any pharmaceutically acceptable oil, and specifically excluding peanut oil, that can suspend or solubilize any suitable progesterone or

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estradiol, starting material, or precursor, including micronized progesterone or estradiol as described herein.

The term “medium chain oil” refers to an oil wherein the composition of the fatty acid fraction of the oil is substantially medium chain (i.e., C6 to C14) fatty acids, i.e., the composition profile of fatty acids in the oil is substantially medium chain. As used herein, “substantially” means that between 20% and 100% (inclusive of the upper and lower limits) of the fatty acid fraction of the oil is made up of medium chain fatty acids, i.e., fatty acids with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. In some embodiments, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 85%, about 90% or about 95% of the fatty acid fraction of the oil is made up of medium chain fatty acids. Those of skill in the art that will readily appreciate that the terms “alkyl content” or “alkyl distribution” of an oil can be used in place of the term “fatty acid fraction” of an oil in characterizing a given oil or solubilizing agent, and these terms are used interchangeable herein. As such, medium chain oils suitable for use in the formulations disclosed herein include medium chain oils wherein the fatty acid fraction of the oil is substantially medium chain fatty acids, or medium chain oils wherein the alkyl content or alkyl distribution of the oil is substantially medium chain alkyls (C6-C12 alkyls). It will be understood by those of skill in the art that the medium chain oils suitable for use in the formulations disclosed herein are pharmaceutical grade (e.g., pharmaceutical grade medium chain oils). Examples of medium chain oils include, for example and without limitation, medium chain fatty acids, medium chain fatty acid esters of glycerol (e.g., for example, mono-, di-, and triglycerides), medium chain fatty acid esters of propylene glycol, medium chain fatty acid derivatives of polyethylene glycol, and combinations thereof.

The term “ECN” or “equivalent carbon number” means the sum of the number of carbon atoms in the fatty acid chains of an oil, and can be used to characterize an oil as, for example, a medium chain oil or a long-chain oil. For example, tripalmitin (tripalmitic glycerol), which is a simple triglyceride containing three fatty acid chains of 16 carbon atoms, has an ECN of $3 \times 16 = 48$. Conversely, a triglyceride with an ECN=40 may have “mixed” fatty acid chain lengths of 8, 16, and 16; 10, 14, and 16; 8, 14, and 18; etc. Naturally occurring oils are frequently “mixed” with respect to specific fatty acids, but tend not to contain both long chain fatty acids and medium chain fatty acids in the same glycerol backbone. Thus, triglycerides with ECNs of 21-42 typically contain predominantly medium chain fatty acids; while triglycerides with ECNs of greater than 43 typically contain predominantly long chain fatty acids. For example, the ECN of corn oil triglyceride in the US Pharmacopeia (USP) would be in the range of 51-54. Medium chain diglycerides with ECNs of 12-28 will often contain predominantly medium chain fatty acids, while diglycerides with ECNs of 32 or greater will typically contain predominantly long chain fatty acids. Monoglycerides will have an ECN that matches the chain length of the sole fatty acid chain. Thus, monoglyceride ECNs in the range of 6-14 contain mainly medium chain fatty acids, and monoglycerides with ECNs 16 or greater will contain mainly long chain fatty acids.

The average ECN of a medium chain triglyceride oil is typically 21-42. For example, as listed in the USP, medium chain triglycerides have the following composition as the exemplary oil set forth in the table below:

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Fatty Acid Tail Length	% of Oil	Exemplary Oil
5	6	≤2.0
	8	50.0-80.0
	10	20.0-50.0
	12	≤3.0
	14	≤1.0

and would have an average ECN of $3 * [(6 * 0.02) + (8 * 0.070) + (10 * 0.25) + (12 * 0.02) + (14 * 0.01)] = 25.8$. The ECN of the exemplary medium chain triglycerides oil can also be expressed as a range (per the ranges set forth in the USP) of 24.9-27.0. For oils that have mixed mono-, di-, and triglycerides, or single and double fatty acid glycols, the ECN of the entire oil can be determined by calculating the ECN of each individual component (e.g., C8 monoglycerides, C8 diglycerides, C10 monoglycerides, and C10 diglycerides) and taking the sum of the relative percentage of the component multiplied by the ECN normalized to a monoglyceride for each component. For example, the oil having C8 and C10 mono- and diglycerides shown in the table below has an ECN of 8.3, and is thus a medium chain oil:

Fatty Acid Chain Length	% of Oil	ECN as % of Oil [(chain length) × (% in oil)]	ECN as % of Oil Normalized to Monoglyceride
C8 monoglyceride	47	$8 \times 0.47 = 3.76$	3.76
C10 monoglyceride	8	$10 \times 0.08 = 0.8$	0.8
C8 diglyceride	38	$2 \times (8 \times 0.38) = 6.08$	$6.08/2 = 3.04$
C10 diglyceride	7	$2 \times (10 \times 0.07) = 1.4$	$1.4/2 = 0.7$
OIL ECN (normalized to monoglycerides)			8.3

Expressed differently, ECN can be calculated as each chain length in the composition multiplied by its relative percentage in the oil: $(8 * 0.85) + (10 * 0.15) = 8.3$.

The term “excipients,” as used herein, refers to non-active pharmaceutical ingredients such as solubilizing agents, antioxidants, oils, lubricants, and others used in formulating pharmaceutical products.

The terms “treat,” “treating,” and “treatment” refer to any indicia of success in the treatment or amelioration of an injury, disease, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, disease, or condition more tolerable to the patient; slowing in the rate of degeneration or decline; or improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subject parameters, including the results of a physical examination, neuropsychiatric examinations, or psychiatric evaluation.

55 II. PHARMACEUTICAL COMPOSITIONS

In one aspect, this disclosure relates to pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof. In some embodiments, the composition comprises estradiol, progesterone, and a solubilizing agent (e.g., a medium chain oil, e.g., a C6-C12 oil). In some embodiments, a pharmaceutical composition comprising estradiol, progesterone, and a solubilizing agent as described herein, when administered to a subject or a population of subjects, produces one or more AUC, C_{max} , or T_{max} parameters for estradiol, progesterone, estrone, or total estrone as described below.

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Formulations of Estradiol and Progesterone Compositions

In some embodiments, a pharmaceutical composition for use as described herein comprises solubilized estradiol with suspended progesterone; solubilized estradiol with both partially solubilized progesterone and partially suspended progesterone; or solubilized estradiol with fully solubilized progesterone. In some embodiments, the composition comprises solubilized estradiol and suspended progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone, although the natural or bio-identical forms of estradiol and progesterone are preferred.

In some embodiments, the composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg. In some embodiments, the composition comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately 80% to 100% soluble in a solubilizing agent, including specifically embodiments that are: 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% soluble in a solubilizing agent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %). In some embodiments, estradiol is micronized. In some embodiments, micronized estradiol has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In some embodiments, micronized estradiol has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. In some embodiments, the composition comprises micronized and partially solubilized estradiol.

In some embodiments, the composition comprises micronized progesterone. The progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size.

Estradiol and progesterone compositions and methods of preparing such compositions are described in U.S. Pat. No. 8,633,178; U.S. Publication No. 2013/0129818; U.S. Publication No. 2013/0338123; International Publication No. WO 2013/078422; and International Publication No. WO 2013/192251; each of which is incorporated by reference in its entirety.

Solubilizing Agents

Estradiol and progesterone compositions of the present disclosure are prepared via blending with a solubilizing agent. In some embodiments, the solubilizing agent is a pharmaceutically acceptable oil that comprises a medium chain oil. In some embodiments, the solubilizing agent is a medium chain oil comprised substantially of C6-C12 medium chains, e.g., at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at

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least 90% of the chains present in the oil are C6-C12. In some embodiments, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids having at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. In some embodiments, the medium chain oil comprises at least one medium chain fatty acid or propylene glycol, polyethylene glycol, or glyceride having esters of medium chain fatty acids. In some embodiments, the solubilizing agent is not peanut oil.

In some embodiments, oils used to solubilize estradiol and to suspend, partially suspend and partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In some embodiments, the medium chain fatty acids are C6, C8, C10, C12, C6-C12, C8-C12, C6-C10, C8-C10, or C10-C12 fatty acids. In some embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 50% saturated, greater than about 60% saturated, or greater than about 75% saturated. In some embodiments, a solubilizing agent comprises predominantly medium chain length, saturated fatty acids or derivatives thereof, specifically predominantly C8 to C12 saturated fatty acids or derivatives thereof.

In some embodiments, medium chain solubilizing agents include, for example and without limitation, saturated medium chain fatty acids or derivatives of saturated medium chain fatty acids: caproic acid (C6), enanthic acid (C7), caprylic acid (C8), pelargonic acid (C9), capric acid (C10), undecylic acid (C11), lauric acid (C12), tridecyllic acid (C13), or myristic acid (C14). In some embodiments, the solubilizing agent comprises oils made of these free medium chain fatty acids, oils of medium chain fatty acid esters of glycerin, propylene glycol, or ethylene glycol, or combinations thereof. These examples comprise predominantly saturated medium chain fatty acids (i.e., greater than 50% of the fatty acids are medium chain saturated fatty acids). In some embodiments, the solubilizing agent comprises predominantly C6 to C12 saturated fatty acids or derivatives of fatty acids.

In some embodiments, the solubilizing agent comprises one or more mono-, di-, or triglycerides or combinations thereof. Exemplary glycerin based solubilizing agents include MIGLYOLS®, which are caprylic/capric triglycerides (SASOL Germany GMBH, Hamburg). MIGLYOLS® includes MIGLYOL® 810 (caprylic/capric triglyceride), MIGLYOL® 812 (caprylic/capric triglyceride), MIGLYOL® 816 (caprylic/capric triglyceride), and MIGLYOL® 829 (caprylic/capric/succinic triglyceride). Other caprylic/capric triglyceride solubilizing agents are likewise contemplated, including, for example: caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; or caprylic/capric/succinic triglycerides. Other exemplary caprylic/capric mono-, di-, or triglyceride solubilizing agents include CAPMULs® (ABITEC, Columbus, Ohio), including, but are not limited to, CAPMUL® MCM, CAPMUL® MCM C10, CAPMUL® MCM C8, CAPMUL® MCM C8 EP, and CAPMUL® 708 G. Other mono-, di-, and triglycerides of fractionated vegetable fatty acids, and combinations or derivatives thereof can be the solubilizing agent, according to embodiments. For example, the solubilizing agent can be 1,2,3-propanetriol (glycerol, glycerin, glycerine) esters of saturated coconut and palm kernel oil and derivatives thereof.

In some embodiments, the solubilizing agent comprises one or more esters of propylene glycol, polyethylene glycol, or combinations thereof. Exemplary propylene and polyeth-

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ylene glycol based solubilizing agents include glyceryl mono- and di-caprylates; propylene glycol monocaprylate (e.g., CAPMUL® PG-8 or CAPMUL® PG-8 NF); propylene glycol monocaprate (e.g., CAPMUL® PG-10); propylene glycol monolaurate (e.g., CAPMUL® PG-12 EP/NF); propylene glycol mono- and dicaprylates; propylene glycol mono- and dicaprate; propylene glycol dicaprylate/dicaprate (e.g., MIGLYOL® 840); propylene glycol dilaurate (e.g., CAPMUL® PG-2L EP/NF); diethylene glycol mono ester (e.g., TRANSCUTOL®, 2-(2-Ethoxyethoxy)ethanol, GATTEFOSSÉ SAS, Saint-Priest, France); and diethylene glycol monoethyl ether.

In some embodiments, commercially available fatty acid glycerol and glycol ester solubilizing agents are prepared from natural oils and therefore may comprise components in addition to the fatty acid esters that predominantly comprise and characterize the solubilizing agent. Such other components may be, e.g., other fatty acid mono-, di-, and triglycerides, fatty acid mono- and diester ethylene or propylene glycols, free glycerols or glycols, or free fatty acids. For example, the Technical Data Sheet by ABITEC for CAP-MUL® MCM C8 describes CAPMUL® MCM C8 as being composed of mono- and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as $\leq 1\%$ C6, $\geq 95\%$ C8, $\leq 5\%$ C10, and $\leq 1.5\%$ C12 and higher. By way of further example, MIGLYOL® 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

In some embodiments, the pharmaceutical composition comprises about 20% to about 85% solubilizing agent by weight, e.g., about 60% to about 85% solubilizing agent by weight. In some embodiments, the composition comprises progesterone, e.g., dissolved and micronized, from about 20 to about 50 wt %, e.g., about 30 to about 35 wt %. In some embodiments, the composition comprises estradiol from about 0.1 to about 0.8 wt %, e.g., about 0.15 to about 0.40 wt %.

Surfactants

In some embodiments, the pharmaceutical composition further comprises one or more non-ionic or ionic surfactants. In some embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of medium chain fatty acids or long chain fatty acids, for example, lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE®, including, for example, GELUCIRE® 39/01 (glycerol esters of saturated C12-C18 fatty acids); GELUCIRE® 43/01 (hard fat NF/JPE); GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, lauroyl polyoxylglycerides (USA FDA IIG)); and GELUCIRE® 50/13 (stearoyl macrogol-32 glycerides EP, stearoyl polyoxyl-32 glycerides NF, stearoyl polyoxylglycerides (USA FDA IIG)).

In some embodiments, non-ionic surfactants comprise combinations of mono- and di-propylene and ethylene glycols and mono-, di-, and triglyceride combinations. For example, in some embodiments, polyethylene glycol glyceride (GELUCIRE®, GATTEFOSSÉ SAS, Saint-Priest, France) can be used herein as the surfactant. For example, GELUCIRE® 44/14 (PEG-32 glyceryl laurate EP), a medium chain fatty acid esters of polyethylene glycol, is a polyethylene glycol glyceride composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

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In some embodiments, non-ionic surfactants include, for example and without limitation: one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In some embodiments, non-ionic surfactants comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids.

In some embodiments, non-ionic surfactants include PEG-6 palmitostearate and ethylene glycol palmitostearate, which are available commercially as TEOFSE® 63 (GATTEFOSSÉ SAS, Saint-Priest, France), which can be used with, for example, CAPMUL® MCM having ratios of MCM to TEOFSE® 63 of, for example, 8:2 or 9:1. Other exemplary solubilizing agents/non-ionic surfactants combinations include, without limitation: MIGLYOL® 812:GELUCIRE 50/13 or MIGLYOL® 812:TEOFSE® 63.

A non-ionic or ionic surfactant may be used at concentrations greater than about 0.01%, for example at a concentration of about 0.01%-10.0%, about 0.1% to 10.0%, or about 1% to 10.0%. In some embodiments, the pharmaceutical composition comprises about 10.0% surfactant by weight. In some embodiments, the pharmaceutical composition comprises about 0.1% to about 5.0% surfactant by weight, e.g., about 1.0 wt %.

Other Excipients

In some embodiments, the pharmaceutical composition further comprises one or more other excipients, such as but not limited to colorants, flavoring agents, preservatives, and taste-masking agents. The choice of excipients will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipients on solubility and stability, and the nature of the dosage form. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Generally, the solubilizing agents, surfactants, and excipients used in the pharmaceutical compositions described herein are non-toxic, pharmaceutically acceptable, compatible with each other, and maintain stability of the pharmaceutical composition and the various components with respect to each other. Additionally, the combination of various components that comprise the pharmaceutical compositions will maintain will result in the desired therapeutic effect when administered to a subject.

Formulation

In some embodiments, combinations of solubilizing agents (e.g., two or more oils) or combinations of one or more solubilizing agents and one or more surfactants are used to form estradiol and progesterone compositions. Various ratios of these solubilizing agents or solubilizing agents and surfactants can be used. For example, CAPMUL® MCM and a non-ionic surfactant, e.g., GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP; lauroyl polyoxyl-32 glycerides NF; lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to about 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. As another example, CAPMUL® MCM and a non-ionic surfactant, e.g., TEOFSE® 63, can be used as ratios of about 8:2 or 9:1. Other exemplary solubilizing agent/surfactant combinations include, without limitation: MIGLYOL® 812:GELUCIRE® 50/13 or MIGLYOL® 812:TEOFSE® 63. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be

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significantly higher. For example, CAPMUL® MCM and GELUCIRE® can be used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1.

In some embodiments, estradiol or progesterone is soluble in the solubilizing agent at room temperature, although it may be desirable to warm certain solubilizing agents. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL® MCM) and polyethylene glycol glycerides (e.g., GELUCIRE®) as a surfactant, the oil or the surfactant can be warmed up, e.g., to about 65° C. for the surfactant and less for the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature, or at lower temperatures as the mixture cools, e.g., about 40° C. or about 30° C., or even after the mixture has cooled to room temperature. The progesterone can also be added as the mixture cools, e.g., to below about 40° C. or to below about 30° C., or after the mixture has cooled to room temperature.

As a non-limiting example, a composition of this disclosure comprises solubilized estradiol; progesterone, at least 30% (e.g., at least about 30%, about 40%, about 50%, about 60%, about 70%, about 75%, about 80%, about 85%, or more) of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein); and a solubilizing agent that is an oil, wherein the oil comprises medium chain fatty acid mono-, di-, or triglycerides, with or without a surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with CAPMUL® MCM NF (glyceryl caprylate/caprate) as a solubilizing agent and GELUCIRE® 44/14 (lauroyl polyoxyglyceride) as a surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following five formulations A-E:

TABLE 1

Pharmaceutical Composition A - progesterone 50 mg/estradiol 0.25 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
CAPMUL ® MCM, NF	65.49	98.24
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

TABLE 2

Pharmaceutical Composition B - progesterone 50 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
CAPMUL ® MCM, NF	65.32	97.98
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

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TABLE 3

Pharmaceutical Composition C - progesterone 100 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
CAPMUL ® MCM, NF	65.49	196.48
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

TABLE 4

Pharmaceutical Composition D - progesterone 100 mg/estradiol 1 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
CAPMUL ® MCM, NF	65.32	195.97
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

*Note:

1.00 mg Estradiol is equivalent to 1.03 mg Estradiol Hemihydrate

TABLE 5

Pharmaceutical Composition E - progesterone 200 mg/estradiol 2 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
CAPMUL ® MCM, NF	65.32	391.94
GELUCIRE ® 44/14, NF	1.00	6.00
Total	100.00	600.00

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono-, di-, or triglycerides, such as CAPMUL® MCM, and 0.5 to 10 wt % of a non-ionic surfactant, such as GELUCIRE® 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, MIGLYOL® 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more, is solubilized appear to provide improved PK-related properties.

60 Pharmacokinetic Parameters of Estradiol and Progesterone Compositions

The pharmaceutical compositions of this disclosure can be formulated to provide desirable pharmacokinetic parameters in a subject (e.g., a female subject) to whom the composition is administered. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for progesterone in the

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subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for estradiol in the subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for one or more metabolites of progesterone or estradiol in the subject, for example, estrone or total estrone.

Following the administration of a composition comprising progesterone and estradiol to a subject, the concentration and metabolism of progesterone or estradiol can be measured in a sample (e.g., a blood, serum, or plasma sample) from the subject. Progesterone is metabolized to pregnane-diols and pregnanolones, which are then conjugated to glucuronide and sulfate metabolites that are excreted or further recycled. Estradiol is converted reversibly to estrone, and both estradiol and estrone can be converted to the metabolite estriol. In postmenopausal women, a significant proportion of circulating estrogens exist as sulfate conjugates, especially estrone sulfate. Thus, estrone can be measured with respect to "estrone" amounts (excluding conjugates such as estrone sulfate) and "total estrone" amounts (including both free, or unconjugated, estrone and conjugated estrone such as estrone sulfate).

The pharmaceutical compositions of this disclosure can be characterized for one or more pharmacokinetic parameters of progesterone, estradiol, or a metabolite thereof following administration of the composition to a subject or to a population of subjects. These pharmacokinetic parameters include AUC, C_{max} , and T_{max} . AUC is a determination of the area under the curve (AUC) plotting the blood, serum, or plasma concentration of drug along the ordinate (Y-axis) against time along the abscissa (X-axis). AUCs are well understood, frequently used tools in the pharmaceutical arts and have been extensively described. C_{max} is well understood in the art as an abbreviation for the maximum drug concentration in blood, serum, or plasma of a subject. T_{max} is well understood in the art as an abbreviation for the time to maximum drug concentration in blood, serum, or plasma of a subject.

In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for estradiol. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for progesterone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for estrone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for total estrone.

Any of a variety of methods can be used for measuring the levels of progesterone, estradiol, estrone, or total estrone in a sample, including immunoassays, mass spectrometry (MS), high performance liquid chromatography (HPLC) with ultraviolet fluorescent detection, liquid chromatography in conjunction with mass spectrometry (LC-MS), tandem mass spectrometry (MS/MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured using a validated LC-MS/MS method. Methods of measuring hormone levels are well described in the literature.

The levels of progesterone, estradiol, estrone, or total estrone can be measured in any biological sample, e.g., a tissue or fluid such as blood, serum, plasma, or urine. In some embodiments, the sample is blood or plasma. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 0.0, 0.10, 0.20, 0.05, 0.30, 0.35, 0.40, 0.45, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15,

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18, 21, 24, 27, 30, 33, 36, 39, 42, 45, or 48 hours after dosing, or any other appropriate time period that is common or useful in determining the levels of each of the hormones. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of a single dose or a first dose. Generally, assays to determine the levels of progesterone, estradiol, estrone, or total estrone are measured one or more times every 5, 10, 15, 20, 30, 60, 120, 360, 480, 720, or 1440 minutes after administration, or combinations thereof (e.g., the first measurements are taken every 15 minutes for the first hour, followed by every 120 minutes thereafter). In embodiments, the timing of such measurements are designed to accurately measure C_{max} , T_{max} , or AUC. Timing can be adjusted based on the given circumstances (i.e., one formulation may cause a more rapid C_{max} , in which case the initial times would be clustered closer together, closer to time zero, or both to ensure accurate measurement of C_{max} , T_{max} , and AUC). In some embodiments, the C_{max} , T_{max} , or AUC values for progesterone, estradiol, estrone, or total estrone are measured following administration of a single dose of a pharmaceutical composition as described herein.

In some embodiments, the values for C_{max} , T_{max} , or AUC represent a number of values taken from all the subjects in a patient population and are, therefore, mean values (e.g., arithmetic or geometric means) averaged over the entire population.

In some embodiments, oral administration of a pharmaceutical composition comprising estradiol, progesterone, and a medium chain solubilizing agent as described herein to a subject, or to a population of subjects, produces one or more AUC, C_{max} , or T_{max} parameters, or one or more mean AUC, mean C_{max} , or mean T_{max} parameters, respectively, for estradiol, progesterone, estrone, or total estrone as described below.

AUC C_{max} , and T_{max} Parameters (A)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation A in Table 1 above.

In some embodiments, administration of a composition comprising about 0.25 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, and a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone

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that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml;

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(ii) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; or

(iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, a mean C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml, a mean C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml, a mean C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone;

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wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; or a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC , C_{max} , and T_{max} Parameters (B)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation B in Table 2 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $(AUC)_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

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In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- 5 (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some

- 20 subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- 45 (i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 pg·hr/ml to 63.0476 pg·hr/ml;
- (ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples

- 55 (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, a mean C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819

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ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, a mean C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

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AUC , C_{max} , and T_{max} Parameters (C)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation C in Table 3 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the

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subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml;
- (ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood and plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, a mean C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation

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C in Table 3 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation C in Table 3 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC , C_{max} , and T_{max} Parameters (D)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation D in Table 4 above.

In some embodiments, administration of a composition comprising about 1 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, and a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

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- (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

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In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml;
- (ii) a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, a mean C_{max} for estradiol

that is from 25.9161 pg/ml to 40.4939 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone

that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567

pg·hr/ml, a mean C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, a mean C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml, and a mean T_{max} for total

estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953

ng·hr/ml; a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the

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pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC, C_{max} , and T_{max} Parameters (E)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation E in Table 5 above.

In some embodiments, administration of a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml; or

(ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml, and a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·h/ml to 150 ng·h/ml; or

(ii) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 96 ng·h/ml to 150 ng·h/ml, and a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

(i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml;

(ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;

(iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·h/ml to 150 ng·h/ml; or

(iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the

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subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

(i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml;

(ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;

(iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·h/ml to 150 ng·h/ml; or

(iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii).

In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some

embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some

embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some

embodiments, administration of the composition to the subject produces both parameters (i), (ii), and (iii). In some

embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some

embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some

embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml;

(ii) a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; or

(iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml

(ii) a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml; or

(iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml, a mean C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 96 ng·h/ml to 150 ng·h/ml, a mean C_{max} for progesterone that is from 71 ng/ml

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to 112 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml; a mean C_{max} for estrone that is from 341 pg/ml to 533 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml; a mean C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml; a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml; a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml; a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml; a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml; a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml; and a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

In some embodiments, administration of the pharmaceutical composition as described herein results in the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, administration of the pharmaceutical composition results in the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, administration of

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the pharmaceutical composition results in the blood plasma estrone concentration profile of FIG. 3. In some embodiments, administration of the pharmaceutical composition results in the blood plasma total estrone concentration profile of FIG. 4.

Administration and Treatment

Pharmaceutical compositions comprising estradiol and progesterone as described herein (e.g., compositions comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent) can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrup, slurries, suspensions, etc., suitable for ingestion by the patient. Pharmaceutical compositions can be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, intrathecal, rectal, vaginal, sublingual or parenteral administration, including subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, or intraurethral injection or infusion. In some embodiments, administration is by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally.

For preparing pharmaceutical compositions from the compounds of this disclosure, the pharmaceutically acceptable compositions can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid preparation can comprise one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. ("Remington's").

In general, the type of composition is selected based on the mode of administration. A pharmaceutical composition (e.g., for oral administration or delivery by injection) can be in the form of a liquid (e.g., an elixir, syrup, solution, emulsion or suspension). Alternatively, a pharmaceutical composition as described herein can take the form of a pill, tablet, or capsule containing the liquid oil, and thus, the composition can contain any of the following: a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof. The composition can also be formulated into a suppository disposed, for example, in a polyethylene glycol (PEG) solubilizing agent.

Administration of the compositions of this disclosure can be carried out via any of the accepted modes of administration. Thus, administration can be, for example, intravenous, topical, subcutaneous, transcutaneous, transdermal, intramuscular, oral, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, or by inhalation. In some embodiments, a composition as described herein is administered orally. For example, a pharmaceutical composition as described herein can be administered via capsules such as soft capsules.

In some embodiments, a pharmaceutical composition as described herein is administered once daily for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 days or more. In some embodiments, a pharmaceutical composition as

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described herein is administered daily for at least one week, at least two weeks, at least three weeks, at least four weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least twelve months, or more. In some embodiments, a pharmaceutical composition as described herein is administered as a continuous-combined therapy regimen.

In some embodiments, a 28-day or monthly regimen of daily doses is packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. In some embodiments, each daily dose contains both estradiol and progesterone. In some embodiments, one or more of the daily doses contains no estradiol or no progesterone. Daily doses that comprise no estradiol or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating the blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized or partially solubilized, or fully solubilized progesterone or solubilized estradiol in amounts as set forth herein, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of daily doses.

In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating conditions in subjects caused, at least in part, by estrogen deficiency, particularly for women with a uterus. For example, in embodiments, the pharmaceutical compositions disclosed herein are useful for the treatment of one or more of the following conditions: endometrial hyperplasia; secondary amenorrhea; prevention of preterm birth, when the subject has a shortened cervix; menopause-related symptoms including, for example, vaso-motor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental progesterone or estrogen. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating vasomotor symptoms, including but not limited to, hot flashes and night sweats. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes and night sweats. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes. Thus, in some embodiments, this disclosure provides methods of treating such a condition by administering to the subject a composition comprising estradiol and progesterone as described herein.

III. EXAMPLES

The following examples are offered to illustrate, but not to limit, the claimed subject matter.

Example 1

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition comprising suspended progesterone and solubilized estradiol:

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TABLE 6

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL® MCM, NF		82.57	577.97
GELUCIRE® 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

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The encapsulated pharmaceutical composition of Table 6 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas (N_2). Mixing or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL® MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.±2° C. GELUCIRE® 44/14 may be added to the CAPMUL® MCM and mixed until dissolved (to increase the solubility of progesterone in the final solution, GELUCIRE® 44/14 was added at about 10% w/w). The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the GELUCIRE® 44/14 and the CAPMUL® MCM.

Heat may be removed from the GELUCIRE® 44/14 and CAPMUL® MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the GELUCIRE® 44/14, CAPMUL® MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 2

An example of the final scale-up formulation is provided in Table 7. To manufacture, CAPMUL® MCM is heated to 40° C. GELUCIRE® 44/14 is heated to 65° C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until fully suspended.

TABLE 7

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL® MCM, NF		82.57	577.97	5.78
4.	GELUCIRE® 44/14, NF		10.0	70.00	0.70
Total: 100.00 700.00 7.00					

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Example 3

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 8

Item No.	Ingredient	Label Claim (mg)	Qty/ % w/w	Amount/ Capsule (mg)	Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL® MCM, NF		73.371	146.74	1467.42
4.	GELUCIRE® 44/14, NF		1.500	3.00	30.00
Total:		100.000	200.00 mg	2000.00	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 4

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 9

Item No.	Ingredient	Label Claim (mg)	Qty/ % w/w	Amount/ Capsule (mg)	Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL® MCM, NF		65.32	391.93	3919.3
4.	GELUCIRE® 44/14, NF		1.00	6.0	60.0
Total:		100.00	600.0 mg	6000.0	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resulting pharmaceutical composition is encapsulated in soft gelatin capsules. Alternatively, GELUCIRE® 44/14 is heated to 65° C. and CAPMUL® MCM is heated to 40° C. \pm 5° C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40° C.; the mixture is then passed through a colloid mill one or more times, e.g., three times.

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Example 5

Pharmacokinetics of the First Combination 17 β -Estradiol/ Progesterone Capsule in Clinical Development for Hormone Therapy

The objective of this study was to evaluate the pharmacokinetic and oral bioavailability of a combination capsule of 17 β -estradiol/progesterone in comparison to co-administration of the individual products ESTRACE® and PROMETRIUM®.

Subjects and Study Design:

An open label, balanced, randomized, single-dose, 2-treatment, 3-period, 3-sequence, crossover, partial-replicate, reference-scaled, oral, relative bioavailability study compared the bioavailability of an investigational 2-mg 17 β -estradiol/200-mg progesterone combination capsule, without peanut oil (formulated in a manner similar to that set forth in Table 9), with that of co-administered 200-mg PROMETRIUM® (progesterone) and 2-mg ESTRACE® (17 β -estradiol) tablets in healthy postmenopausal women aged 40-65 years (N=66). Key inclusion criteria for subjects included a BMI 18.50 to 29.99 kg/m² who were nonsmokers or ex-smokers (no smoking in the last 3 months). Key exclusion criteria for subjects included consuming grapefruit juice or poppy-containing foods within 48 hours before and throughout the study, use of any hormonal agent within 14 days before the study, and use of menopausal hormone therapy within 6 months before dosing.

Patients were randomly assigned sequentially to 1 of 3 dosing sequences of the same dose of the combination capsule (Test, T) and reference products (Reference, R): TRR, RTR, or RRT. 66 subjects were randomized and 62 (94.0%) completed the study. Subjects had a mean age of 49.5 \pm 5.6 years (range 40 to 64) and a mean BMI of 24.8 \pm 3.1 kg/m² (range 18.7-29.9).

After consuming a high-fat, high-calorie breakfast, each woman received a single dose of the combination (Test) capsule in 1 period of the study and single doses of the co-administered products (Reference) in each of the 2 remaining periods. Blood samples were collected within 75 minutes before dosing and post-dose at 0.25, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 hours after dosing to determine progesterone, free (unconjugated) estradiol, and free and total (conjugated+free) including estrone sulfates) estrone concentrations. After collection of blood samples at each time point, the blood samples were centrifuged at 4000 RPM for 10 minutes at 4° C. to separate the plasma. The plasma from samples was separated into two aliquots. 1.5 mL from the plasma sample was transferred into aliquot I, and the remaining plasma sample was transferred into aliquot II. These aliquots were stored at -30° C. for interim storage, then at -70° C. until completion of the analysis.

Progesterone, estradiol, estrone, and total estrone in human plasma was determined using the LC-MS/MS method. The primary (C_{max} , AUC_{0-t} and $AUC_{0-\infty}$) and secondary (T_{max} , $t_{1/2}$, and K_e) PK parameters for each analyte were determined for each subject during each period by non-compartment analyses using baseline-adjusted concentrations. Statistical analyses were conducted using the SAS® statistical software.

Results: The mean, standard deviation (SD), geometric mean, coefficient of variation (CV %), minimum, median, and maximum were calculated for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, K_e , K_{el_lower} , K_{el_Upper} and $AUC\%Extrap_obs$ for progesterone, estradiol, estrone, and total estrone. The results are presented in Tables 10, 11, 12, and 13 below. For each of Tables 10-13, "Test Product (T)" refers to the progesterone+estradiol pharmaceutical composition, while "Reference product (R1)" and "Reference product (R2)" refers to co-administered PROMETRIUM® (progesterone) and ESTRACE® (estradiol). Blood plasma concentrations of progesterone, estradiol, estrone, and total estrone over time are also shown in FIGS. 1-4.

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TABLE 10

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R₁, R₂) for Progesterone

PK Parameter	Untransformed Data (Mean ± SD)					
	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
C _{max} (ng/mL)	62	89.2222 ± 149.7309	62	72.7228 ± 101.8885	62	69.7590 ± 87.0777
AUC _{0-t} (ng · hr/mL)	62	120.0869 ± 164.1385	62	125.9406 ± 152.3483	62	111.5867 ± 113.3200
AUC _{0-∞} (ng · hr/mL)	57	131.3817 ± 172.4806	57	142.1332 ± 160.4853	56	126.6006 ± 117.2665
T _{max} (hr)	62	3.00 (0.83-10.00)	62	3.00 (1.00-12.00)	62	4.00 (0.67-18.00)
K _{el} (hr ⁻¹)	57	0.3064 ± 0.2427	57	0.2684 ± 0.1912	56	0.2795 ± 0.2475
t _{1/2} (hr)	57	4.6445 ± 4.5366	57	5.1555 ± 4.9794	56	5.0389 ± 4.5887
K _{el_Lower} (hr ⁻¹)	57	7.6667 ± 4.6047	57	7.4123 ± 4.2164	56	7.9018 ± 3.9120
K _{el_Upper} (hr ⁻¹)	57	16.2218 ± 11.0051	57	19.1728 ± 12.3801	56	18.1975 ± 10.0858
AUC_Extra (%)	57	4.3374 ± 2.5528	57	4.8416 ± 3.7526	56	5.1868 ± 4.1434

*Expressed in terms of median (range)

TABLE 11

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R₁, R₂) for Estradiol

PK Parameter	Untransformed Data (Mean ± SD)		
	Test Product (T)	Reference product (R1)	Reference product (R2)
C _{max} (pg/mL)	64.7902 ± 50.9833	69.1286 ± 33.0484	73.4236 ± 43.4077
AUC _{0-t} (pg · hr/mL)	1403.7333 ± 763.8136	1508.2206 ± 876.7390	1658.2502 ± 976.5556
AUC _{0-∞} (pg · hr/mL)	2459.4394 ± 4498.2737	2842.8805 ± 4582.6502	2110.9591 ± 1175.3995
T _{max} (hr)	9.00(0.50-36.00)	10.00(0.50-35.12)	10.00(0.25-36.60)
K _{el} (hr ⁻¹)	0.0438 ± 0.0197	0.0457 ± 0.0358	0.0464 ± 0.0338
t _{1/2} (hr)	31.9104 ± 95.9769	25.0908 ± 28.8346	20.8774 ± 12.0825
K _{el_Lower} (hr ⁻¹)	14.9472 ± 7.2715	14.9667 ± 7.0150	14.7953 ± 5.8774
K _{el_Upper} (hr ⁻¹)	45.3602 ± 6.3668	44.3277 ± 7.4003	43.8330 ± 7.6449
AUC_Extra (%)	22.8106 ± 16.6498	25.4773 ± 20.2911	24.9566 ± 16.4713

*Expressed in terms of median (range)

TABLE 12

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R₁, R₂) for Free Estrone

PK Parameter	Untransformed Data (Mean ± SD)		
	Test Product (T)	Reference product (R1)	Reference product (R2)
C _{max} (pg/mL)	426.5492 ± 179.3303	455.5107 ± 189.448	467.2302 ± 207.4373
AUC _{0-t} (pg · hr/mL)	9096.0907 ± 4377.2730	10156.0282 ± 5140.5831	10507.3557 ± 5183.1289
AUC _{0-∞} (pg · hr/mL)	11994.9695 ± 6678.5468	13445.9048 ± 8699.4068	14066.2362 ± 7563.2370
T _{max} (hr)	5.50(0.83-36.00)	8.00(1.67-18.00)	10.00(1.67-18.00)
K _{el} (hr ⁻¹)	0.0399 ± 0.0146	0.0424 ± 0.0172	0.0406 ± 0.0209
t _{1/2} (hr)	20.3172 ± 9.4052	19.4595 ± 9.8711	20.7515 ± 9.3985
K _{el_Lower} (hr ⁻¹)	13.8443 ± 7.0649	14.8871 ± 6.6459	14.9194 ± 6.4485
K _{el_Upper} (hr ⁻¹)	46.0238 ± 5.5080	46.2547 ± 5.3060	46.2244 ± 5.3126
AUC_Extra (%)	21.2980 ± 11.2283	20.3648 ± 11.1060	21.8900 ± 11.8537

*Expressed in terms of median (range)

TABLE 13

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R₁, R₂) for Total Estrone

PK Parameter	Untransformed Data (Mean ± SD)					
	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
C _{max} (ng/mL)	61	35.4289 ± 17.0856	61	19.8716 ± 7.4485	61	19.9048 ± 8.0288
AUC _{0-t} (ng · hr/mL)	61	201.7524 ± 94.2081	61	182.7729 ± 88.8386	61	199.8295 ± 94.9392
AUC _{0-∞} (ng · hr/mL)	61	213.2402 ± 104.6011	60	193.6387 ± 100.5831	56	203.0289 ± 81.4884
T _{max} (hr)	61	2.50 (0.67-7.00)	61	4.00 (1.33-18.00)	61	4.00 (1.33-10.00)

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TABLE 13-continued

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Total Estrone						
PK Parameter	Untransformed Data (Mean ± SD)		N	Reference product (R1)	N	Reference product (R2)
	N	Test Product (T)				
K _{el} (hr ⁻¹)	61	0.0799 ± 0.0398	60	0.0803 ± 0.0399	56	0.0718 ± 0.0243
t _{1/2} (hr)	61	10.3619 ± 4.0023	60	9.8448 ± 3.0702	56	10.7830 ± 3.6624
K _{el_Lower} (hr ⁻¹)	61	13.0492 ± 6.8585	60	13.5945 ± 8.0129	56	11.8870 ± 6.8696
K _{el_Upper} (hr ⁻¹)	61	45.3979 ± 6.6589	60	46.3775 ± 5.2525	56	46.7054 ± 4.3888
AUC_Extra (%)	61	4.5030 ± 3.7366	60	4.5913 ± 3.4953	56	5.3450 ± 3.9831

*Expressed in terms of median (range)

Example 6

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Pharmacokinetic data (C_{max}, AUC_(0-t), AUC_(0-∞), and T_{max}) for progesterone, estradiol, free estrone, and total estrone is presented in Tables 14-17. Pharmaceutical compositions A-E are disclosed in Tables 1-5. The pK values for pharmaceutical composition E were calculated as disclosed in Example 5. For pharmaceutical compositions A-D, expected pharmacokinetic data is calculated from the data disclosed for pharmaceutical composition E.

TABLE 14

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Progesterone						
Pharma-	Proges-	Estradiol	C _{max}	AUC _(0-t)	AUC _(0-∞)	T _{max}
ceutical	terone	Content	(ng/mL)	(ng · hr/ mL)	(ng · hr/ mL)	(hr)
A	50 mg	0.25 mg	22.30555	30.0217	32.8454	3.00
B	50 mg	0.50 mg	22.3055	30.0217	32.8454	3.00
C	100 mg	0.50 mg	44.6111	60.0435	65.6909	3.00
D	100 mg	1 mg	44.6111	60.0435	65.6909	3.00
E	200 mg	2 mg	89.2222	120.0869	131.3817	3.00

TABLE 15

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Estradiol						
Pharma-	Proges-	Estradiol	C _{max}	AUC _(0-t)	AUC _(0-∞)	T _{max}
ceutical	terone	Content	(pg/mL)	(pg · hr/mL)	(pg · hr/mL)	(hr)
A	50 mg	0.25 mg	8.0988	175.4667	307.4299	9.00
B	50 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
C	100 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
D	100 mg	1 mg	32.3951	701.8667	1229.7197	9.00
E	200 mg	2 mg	64.7902	1403.7333	2459.4394	9.00

TABLE 16

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Free Estrone						
Pharma-	Proges-	Estradiol	C _{max}	AUC _(0-t)	AUC _(0-∞)	T _{max}
ceutical	terone	Content	(pg/mL)	(pg · hr/ mL)	(pg · hr/ mL)	(hr)
A	50 mg	0.25 mg	53.3187	1137.0113	1499.3712	5.50
B	50 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
C	100 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
D	100 mg	1 mg	213.2746	4548.0454	5997.4848	5.50
E	200 mg	2 mg	426.5492	9096.0907	11994.9695	5.50

TABLE 17

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Total Estrone						
Pharma-	Proges-	Estradiol	C _{max}	AUC _(0-t)	AUC _(0-∞)	T _{max}
ceutical	terone	Content	(ng/mL)	(ng · hr/mL)	(ng · hr/mL)	(hr)
A	50 mg	0.25 mg	4.4286	25.2191	26.6550	2.50
B	50 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
C	100 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
D	100 mg	1 mg	17.7145	100.8762	106.6201	2.50
E	200 mg	2 mg	35.4289	201.7524	213.2402	2.50

The ranges of expected pK values for each of the pharmaceutical compositions of Tables 1-4 are disclosed in Tables 18-21, respectively.

TABLE 18

pK Ranges for the Pharmaceutical Composition of Table 1 (Pharmaceutical Composition A)				
	C _{max}	AUC _(0-t)	AUC _(0-∞)	
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL	
Estradiol	6.4790 pg/mL to 10.1235 pg/mL	140.3733 pg · hr/mL to 219.3333 pg · hr/mL	245.9439 pg · hr/mL to 384.2874 pg · hr/mL	
Free estrone	42.6549 pg/mL to 66.6483 pg/mL	909.6091 pg · hr/mL to 1421.2642 pg · hr/mL	1199.4970 pg · hr/mL to 1874.2140 pg · hr/mL	

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TABLE 18-continued

pK Ranges for the Pharmaceutical Composition of Table 1 (Pharmaceutical Composition A)			
	C _{max}	AUC _(0-t)	AUC _(0-∞)
Total estrone	3.5429 ng/mL to 5.5358 ng/mL	20.1752 ng · hr/mL to 31.5238 ng · hr/mL	21.3240 ng · hr/mL to 33.3188 ng · hr/mL

TABLE 19

pK Ranges for the Pharmaceutical Composition of Table 2 (Pharmaceutical Composition B)			
	C _{max}	AUC _(0-t)	AUC _(0-∞)
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

TABLE 20

pK Ranges for the Pharmaceutical Composition of Table 3 (Pharmaceutical Composition C)			
	C _{max}	AUC _(0-t)	AUC _(0-∞)
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

TABLE 21

pK Ranges for the Pharmaceutical Composition of Table 4 (Pharmaceutical Composition D)			
	C _{max}	AUC _(0-t)	AUC _(0-∞)
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	25.9161 pg/mL to 40.4939 pg/mL	561.4933 pg · hr/mL to 877.3333 pg · hr/mL	983.7758 pg · hr/mL to 1537.1496 pg · hr/mL
Free estrone	170.6197 pg/mL to 266.5933 pg/mL	3638.4363 pg · hr/mL to 5685.0567 pg · hr/mL	4797.9878 pg · hr/mL to 7496.8559 pg · hr/mL
Total estrone	14.1716 ng/mL to 22.1431 ng/mL	80.7010 ng · hr/mL to 126.0953 ng · hr/mL	85.2961 ng · hr/mL to 133.2751 ng · hr/mL

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various

alternatives together with details of the structure and function of the devices or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the

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appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 0.25 mg estradiol, wherein at least 80% of the 10 estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

a medium-chain oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; and (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

2. The method of claim 1, wherein the subject is female.

3. The method of claim 1, wherein the subject is a woman having a uterus.

4. The method of claim 1, wherein administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

5. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

6. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; and (ii) a C_{max} for estrone that is from 42.6549 pg/ml to 50.66.6483 pg/ml.

7. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and (ii) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

8. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 0.5 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

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a medium-chain oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; and (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

9. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; and (ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

10. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and (ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

11. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

12. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 1 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

a medium-chain (C6-C12) oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; and (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

13. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; and

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(i) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml.

14. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and

(ii) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

15. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and

(ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

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16. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

5 (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and

(ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

17. The method of claim 1, wherein the composition comprises about 0.25 mg estradiol and about 50 mg progesterone.

18. The method of claim 8, wherein the composition comprises about 0.5 mg estradiol and about 50 mg progesterone.

19. The method of claim 8, wherein the composition comprises about 0.5 mg estradiol and about 100 mg progesterone.

20. The method of claim 12, wherein the composition comprises about 1 mg estradiol and about 100 mg progesterone.

* * * * *

EXHIBIT M



US010639375B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 10,639,375 B2
(45) **Date of Patent:** *May 5, 2020

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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- (63) Continuation of application No. 14/125,547, filed as application No. PCT/US2013/046442 on Jun. 18, 2013, now Pat. No. 10,052,386, which is a continuation of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178, which is a continuation-in-part of application No. 13/843,428, filed on Mar. 15, 2013, now Pat. No. 9,301,920, which is a continuation of application No. PCT/US2013/023309, filed on Jan. 25, 2013, which is a continuation of application No. 13/843,362, filed on Mar. 15, 2013.
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(56)

References Cited

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934 Dolay
2,232,438 A	2/1941 Butenandt
2,379,832 A	7/1945 Serini et al.
2,649,399 A	8/1953 Beall et al.
3,198,707 A	8/1965 Nomine et al.
3,478,070 A	11/1969 Stein et al.
3,526,648 A	9/1970 Bertin et al.
3,710,795 A	1/1973 Higuchi et al.
3,729,560 A	4/1973 Hagerman
3,729,566 A	4/1973 Ericsson et al.
3,755,573 A	8/1973 Berman
3,755,575 A	8/1973 Lerner
3,903,880 A	9/1975 Higuchi et al.
3,916,898 A	11/1975 Robinson
3,916,899 A	11/1975 Theeuwes et al.
3,921,636 A	11/1975 Zaffaroni
3,923,997 A	12/1975 Meuly
3,948,254 A	4/1976 Zaffaroni
3,971,367 A	7/1976 Zaffaroni
3,977,404 A	8/1976 Theeuwes
3,993,072 A	11/1976 Zaffaroni
4,008,719 A	2/1977 Theeuwes et al.
4,012,496 A	3/1977 Schopflin et al.
4,014,334 A	3/1977 Theeuwes et al.
4,014,987 A	3/1977 Heller et al.
4,016,251 A	4/1977 Higuchi et al.
4,071,623 A	1/1978 van der Vies

(Continued)

FOREIGN PATENT DOCUMENTS

BR	P1 1001367-9 A2	7/2012
CA	2548281 A1	6/2005

(Continued)

OTHER PUBLICATIONS

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)

(Continued)

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(57) **ABSTRACT**

Various pharmaceutical formulations are disclosed herein. For example, a pharmaceutical formulation is disclosed comprising ultra-micronized progesterone.

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Page 2

(56)	References Cited			
U.S. PATENT DOCUMENTS				
4,093,709 A	6/1978	Choi et al.	5,653,983 A	8/1997 Meybeck et al.
4,154,820 A	5/1979	Simoons	5,656,286 A	8/1997 Miranda et al.
4,155,991 A	5/1979	Schopflin et al.	5,660,839 A	8/1997 Allec et al.
4,196,188 A	4/1980	Besins	5,662,927 A	9/1997 Ehrlich et al.
4,215,691 A	8/1980	Wong	5,663,160 A	9/1997 Meybeck et al.
4,237,885 A	12/1980	Wong et al.	5,676,968 A	10/1997 Lipp et al.
4,310,510 A	1/1982	Sherman et al.	5,677,292 A	10/1997 Li et al.
4,327,725 A	5/1982	Cortese et al.	5,686,097 A	11/1997 Taskovich et al.
4,372,951 A	2/1983	Vorys	5,693,335 A	12/1997 Xia et al.
4,384,096 A	5/1983	Sonnabend	5,694,947 A	12/1997 Lehtinen et al.
4,393,871 A	7/1983	Vorhauer et al.	5,700,480 A	12/1997 Hille et al.
4,402,695 A	9/1983	Wong	5,709,844 A	1/1998 Arbeit et al.
4,423,151 A	12/1983	Baranczuk	5,719,197 A	2/1998 Kanios et al.
4,449,980 A	5/1984	Millar et al.	5,735,801 A	4/1998 Caillouette
4,610,687 A	9/1986	Fogwell	5,739,176 A	4/1998 Dunn et al.
4,629,449 A	12/1986	Wong	5,744,463 A	4/1998 Bair
4,732,763 A	3/1988	Beck et al.	5,747,058 A	5/1998 Tipton
4,738,957 A	4/1988	Laurent et al.	5,762,614 A	6/1998 Caillouette
4,756,907 A	7/1988	Beck et al.	5,770,176 A	6/1998 Nargessi
4,762,717 A	8/1988	Crowley, Jr.	5,770,219 A	6/1998 Chiang
4,788,062 A	11/1988	Gale et al.	5,770,220 A	6/1998 Meconi et al.
4,816,257 A	3/1989	Buster et al.	5,770,227 A	6/1998 Dong et al.
4,822,616 A	4/1989	Zimmermann et al.	5,776,495 A	7/1998 Duclos et al.
4,865,848 A	9/1989	Cheng et al.	5,780,044 A	7/1998 Yewey et al.
4,900,734 A	2/1990	Maxson et al.	5,780,050 A	7/1998 Jain et al.
4,906,475 A	3/1990	Kim	5,788,980 A	8/1998 Nabahi
4,942,158 A	7/1990	Sarpotdar et al.	5,788,984 A	8/1998 Guenther et al.
4,961,931 A	10/1990	Wong	5,789,442 A	8/1998 Garfield et al.
5,030,629 A	7/1991	Rajadhyaksha	5,811,416 A	9/1998 Chwalisz et al.
5,064,654 A	11/1991	Berner et al.	5,811,547 A	9/1998 Nakamichi et al.
5,108,995 A	4/1992	Casper	5,814,329 A	9/1998 Shah
5,128,138 A	7/1992	Blank	5,820,878 A	10/1998 Hirano et al.
5,130,137 A	7/1992	Crowley, Jr.	5,827,200 A	10/1998 Caillouette
5,140,021 A	8/1992	Maxson et al.	5,840,327 A	11/1998 Gale et al.
5,211,952 A	5/1993	Spicer et al.	5,843,468 A	12/1998 Burkoth et al.
5,252,334 A	10/1993	Chiang et al.	5,843,979 A	12/1998 Wille et al.
5,280,023 A	1/1994	Ehrlich et al.	5,858,394 A	1/1999 Lipp et al.
5,288,496 A	2/1994	Lewis	5,863,552 A	1/1999 Yue
5,340,584 A	8/1994	Spicer et al.	5,866,603 A	2/1999 Li et al.
5,340,585 A	8/1994	Pike et al.	5,882,676 A	3/1999 Lee et al.
5,340,586 A	8/1994	Pike et al.	5,885,612 A	3/1999 Meconi et al.
5,362,497 A	11/1994	Yamada et al.	5,888,533 A	3/1999 Dunn
5,382,573 A	1/1995	Casper	5,891,462 A	4/1999 Carrara
5,393,528 A	2/1995	Staab	5,891,868 A	4/1999 Cummings et al.
5,393,529 A	2/1995	Hoffmann et al.	5,898,038 A	4/1999 Yallampalli et al.
5,419,910 A	5/1995	Lewis	5,902,603 A	5/1999 Chen et al.
5,468,736 A	11/1995	Hodgen	5,904,931 A	5/1999 Lipp et al.
5,474,783 A	12/1995	Miranda et al.	5,906,830 A	5/1999 Farinas et al.
5,480,776 A	1/1996	Dullien	5,912,010 A	6/1999 Wille et al.
5,514,673 A	5/1996	Heckenmueller et al.	5,916,176 A	6/1999 Caillouette
5,516,528 A	5/1996	Hughes et al.	RE36,247 E	7/1999 Plunkett et al.
5,527,534 A	6/1996	Myhling	5,919,477 A	7/1999 Bevan et al.
5,529,782 A	6/1996	Staab	5,922,349 A	7/1999 Elliesen et al.
5,538,736 A	7/1996	Hoffmann et al.	5,928,666 A	7/1999 Farinas et al.
5,543,150 A	8/1996	Bologna et al.	5,942,243 A	8/1999 Shah
5,547,948 A	8/1996	Barcomb	5,952,000 A	9/1999 Venkateshwaran et al.
5,556,635 A	9/1996	Istin et al.	5,958,446 A	9/1999 Miranda et al.
5,565,199 A	10/1996	Page et al.	5,962,445 A	10/1999 Stewart
5,567,831 A	10/1996	Li	5,968,919 A	10/1999 Samour et al.
5,569,652 A	10/1996	Beier et al.	5,972,372 A	10/1999 Saleh et al.
5,580,572 A	12/1996	Mikler et al.	5,985,311 A	11/1999 Cordes et al.
5,582,592 A	12/1996	Kendrick	5,985,850 A	11/1999 Falk et al.
5,585,370 A	12/1996	Casper	5,985,861 A	11/1999 Levine et al.
5,595,759 A	1/1997	Wright et al.	5,989,568 A	11/1999 Breton et al.
5,595,970 A	1/1997	Garfield et al.	5,993,856 A	11/1999 Ragavan et al.
5,605,702 A	2/1997	Teillaud et al.	6,001,846 A	12/1999 Edwards et al.
5,607,691 A	3/1997	Hale et al.	6,007,835 A	12/1999 Bon-Lapillon et al.
5,607,693 A	3/1997	Bonte et al.	6,010,715 A	1/2000 Wick et al.
5,609,617 A	3/1997	Shealy et al.	6,013,276 A	1/2000 Math et al.
5,620,705 A	4/1997	Dong et al.	6,022,562 A	2/2000 Autant et al.
5,626,866 A	5/1997	Ebert et al.	6,024,974 A	2/2000 Li
5,629,021 A	5/1997	Wright	6,024,976 A	2/2000 Miranda et al.
5,633,011 A	5/1997	Dong et al.	6,056,972 A	5/2000 Hermsmeyer
5,633,242 A	5/1997	Oettel	6,060,077 A	5/2000 Meignant
5,639,743 A	6/1997	Kaswan et al.	6,068,853 A	5/2000 Giannos et al.

US 10,639,375 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

6,074,625 A	6/2000	Hawthorne et al.	6,468,526 B2	10/2002	Chrisope
6,077,531 A	6/2000	Salin-Drouin	6,469,016 B1	10/2002	Place et al.
6,080,118 A	6/2000	Blythe	6,472,434 B1	10/2002	Place et al.
6,083,178 A	7/2000	Caillouette	6,479,232 B1	11/2002	Howett et al.
6,086,916 A	7/2000	Agnus et al.	6,495,160 B2	12/2002	Esposito et al.
6,087,352 A	7/2000	Trout	6,500,814 B1	12/2002	Hesch
6,090,404 A	7/2000	Meconi et al.	6,503,896 B1	1/2003	Tanabe et al.
6,096,338 A	8/2000	Lacy et al.	6,511,969 B1	1/2003	Hermsmeyer
6,106,848 A	8/2000	Preuilh et al.	6,521,250 B2	2/2003	Meconi et al.
6,117,446 A	9/2000	Place	6,526,980 B1	3/2003	Tracy et al.
6,117,450 A	9/2000	Dittgen et al.	6,528,094 B1	3/2003	Savoir et al.
6,124,362 A	9/2000	Bradbury et al.	6,531,149 B1	3/2003	Kirstgen et al.
6,133,251 A	10/2000	Dittgen et al.	6,537,580 B1	3/2003	Savoir et al.
6,133,320 A	10/2000	Yallampalli et al.	6,538,039 B2	3/2003	Laurent
6,139,868 A	10/2000	Hoffmann	6,544,196 B2	4/2003	Caillouette
6,139,873 A	10/2000	Hughes, Jr. et al.	6,544,553 B1	4/2003	Hsia et al.
6,149,935 A	11/2000	Chiang et al.	6,548,053 B1	4/2003	Stewart et al.
6,153,216 A	11/2000	Cordes et al.	6,548,491 B2	4/2003	Tanabe et al.
6,165,491 A	12/2000	Grasset et al.	6,551,611 B2	4/2003	Elliesen et al.
6,165,975 A	12/2000	Adams et al.	6,555,131 B1	4/2003	Wolff et al.
6,187,323 B1	2/2001	Aiache et al.	6,562,367 B1	5/2003	Wolff et al.
6,187,339 B1	2/2001	de Haan et al.	6,562,370 B2	5/2003	Luo et al.
6,190,331 B1	2/2001	Caillouette	6,562,790 B2	5/2003	Chein et al.
6,201,072 B1	3/2001	Rathi et al.	6,569,463 B2	5/2003	Patel et al.
6,217,886 B1	4/2001	Önyüksel et al.	6,583,129 B1	6/2003	Mazer et al.
6,225,297 B1	5/2001	Stockemann et al.	6,586,006 B2	7/2003	Roser et al.
6,227,202 B1	5/2001	Matapurkar	6,589,549 B2	7/2003	Shin et al.
6,228,383 B1	5/2001	Hansen et al.	6,593,317 B1	7/2003	de Ziegler et al.
6,228,852 B1	5/2001	Shaak	6,599,519 B1	7/2003	Seo et al.
6,242,509 B1	6/2001	Berger et al.	6,610,652 B2	8/2003	Adams et al.
6,245,811 B1	6/2001	Horrobin et al.	6,610,670 B2	8/2003	Backensfeld et al.
6,262,115 B1	7/2001	Guittard et al.	6,610,674 B1	8/2003	Schreiber
6,264,980 B1	7/2001	Hille	6,635,274 B1	10/2003	Masiz et al.
6,267,984 B1	7/2001	Beste et al.	6,638,528 B1	10/2003	Kanios
6,274,165 B1	8/2001	Meconi et al.	6,638,536 B2	10/2003	Savoir et al.
6,277,418 B1	8/2001	Marakverich et al.	6,645,528 B1	11/2003	Straub et al.
6,283,927 B1	9/2001	Caillouette	6,649,155 B1	11/2003	Dunlop et al.
6,287,588 B1	9/2001	Shih et al.	6,653,298 B2	11/2003	Potter et al.
6,287,693 B1	9/2001	Savoir et al.	6,656,929 B1	12/2003	Agnus et al.
6,294,188 B1	9/2001	Raga Van et al.	6,660,726 B2	12/2003	Hill et al.
6,294,192 B1	9/2001	Patel et al.	6,663,608 B2	12/2003	Rathbone et al.
6,294,550 B1	9/2001	Place et al.	6,663,895 B2	12/2003	Savoir et al.
6,299,900 B1	10/2001	Reed et al.	6,682,757 B1	1/2004	Wright
6,303,132 B1	10/2001	Nelson	6,692,763 B1	2/2004	Cummings et al.
6,303,588 B1	10/2001	Danielov	6,708,822 B1	3/2004	Muni
6,306,841 B1	10/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.
6,306,914 B1	10/2001	de Ziegler et al.	6,737,081 B2	5/2004	Savoir et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,740,333 B2	5/2004	Becket et al.
6,309,848 B1	10/2001	Howett et al.	6,743,448 B2	6/2004	Kryger
6,312,703 B1	11/2001	Orthofer	6,743,815 B2	6/2004	Huebner et al.
6,328,987 B1	12/2001	Marini	6,747,018 B2	6/2004	Tanabe et al.
6,342,491 B1	1/2002	Dey et al.	6,750,291 B2	6/2004	Kim et al.
6,344,211 B1	2/2002	Hille	6,756,208 B2	6/2004	Griffin et al.
6,372,209 B1	4/2002	Chrisope	6,776,164 B2	8/2004	Bunt et al.
6,372,245 B1	4/2002	Bowman et al.	6,787,152 B2	9/2004	Kirby et al.
6,372,246 B1	4/2002	Wei et al.	6,805,877 B2	10/2004	Massara et al.
6,387,390 B1	5/2002	Deaver et al.	6,809,085 B1	10/2004	Elson et al.
6,402,705 B1	6/2002	Caillouette	6,818,226 B2	11/2004	Reed et al.
6,416,778 B1	7/2002	Raga Van et al.	6,821,524 B2	11/2004	Marini
6,420,352 B1	7/2002	Knowles	6,841,716 B1	1/2005	Tsutsumi
6,423,039 B1	7/2002	Rathbone et al.	6,844,334 B2	1/2005	Hill et al.
6,423,683 B1	7/2002	Heaton et al.	6,855,703 B1	2/2005	Hill et al.
6,432,438 B1	8/2002	Shukla	6,860,859 B2	3/2005	Mehrotra et al.
6,436,633 B1	8/2002	Kreider et al.	6,866,865 B2	3/2005	Hsia et al.
6,440,454 B1	8/2002	Santoro et al.	6,869,969 B2	3/2005	Heubner et al.
6,444,224 B1	9/2002	Rathbone et al.	6,878,518 B2	4/2005	Whitehead
6,444,234 B1	9/2002	Kirby et al.	6,901,278 B1	5/2005	Notelovitz
6,451,300 B1	9/2002	Dunlop et al.	6,905,705 B2	6/2005	Palm et al.
6,451,339 B2	9/2002	Patel et al.	6,911,211 B2	6/2005	Eini et al.
6,451,779 B1	9/2002	Hesch	6,911,438 B2	6/2005	Wright
6,455,246 B1	9/2002	Howett et al.	6,923,988 B2	8/2005	Patel et al.
6,455,517 B1	9/2002	Tanabe et al.	6,924,274 B2	8/2005	Lardy et al.
6,465,004 B1	10/2002	Rossi-Montero et al.	6,932,983 B1	8/2005	Straub et al.
6,465,005 B1	10/2002	Biali et al.	6,939,558 B2	9/2005	Massara et al.
6,465,006 B1	10/2002	Zhang et al.	6,943,021 B2	9/2005	Klausner et al.
			6,958,327 B1	10/2005	Hillisch et al.
			6,960,337 B2	11/2005	Daniels et al.
			6,962,691 B1	11/2005	Lulla et al.
			6,962,908 B2	11/2005	Aloba et al.

US 10,639,375 B2

Page 4

(56)	References Cited						
U.S. PATENT DOCUMENTS							
6,967,194	B1	11/2005	Matsuo et al.	7,829,115	B2	11/2010	Besins et al.
6,974,569	B2	12/2005	Dunlop et al.	7,829,116	B2	11/2010	Griswold et al.
6,977,250	B2	12/2005	Rodriguez	RE42,012	E	12/2010	Deaver et al.
6,978,945	B2	12/2005	Wong	7,850,992	B2	12/2010	Kim et al.
6,995,149	B1	2/2006	Endrikat et al.	7,854,753	B2	12/2010	Kraft et al.
7,004,321	B1	2/2006	Palm et al.	7,858,607	B2	12/2010	Mamchur
7,005,429	B2	2/2006	Dey et al.	RE42,072	E	1/2011	Deaver et al.
7,011,846	B2	3/2006	Shojaei et al.	7,862,552	B2	1/2011	McIntyre et al.
7,018,992	B2	3/2006	Koch et al.	7,867,990	B2	1/2011	Schultz et al.
7,030,104	B2	4/2006	Gray et al.	7,871,643	B2	1/2011	Lizio et al.
7,030,157	B2	4/2006	Ke et al.	7,879,830	B2	2/2011	Wiley
RE39,104	E	5/2006	Duclos et al.	7,884,093	B2	2/2011	Creasy et al.
7,074,779	B2	7/2006	Sui et al.	7,925,519	B2	4/2011	Greene
7,083,590	B1	8/2006	Bunt et al.	7,939,104	B2	5/2011	Barbera et al.
7,091,213	B2	8/2006	Metcalf, III et al.	7,943,602	B2	5/2011	Bunschoten et al.
7,094,228	B2	8/2006	Zhang et al.	7,943,604	B2	5/2011	Coelingh Bennink et al.
7,097,853	B1	8/2006	Garbe et al.	7,945,459	B2	5/2011	Grace et al.
7,101,342	B1	9/2006	Caillouetie	7,960,368	B2	6/2011	Nickisch et al.
7,105,573	B2	9/2006	Krajcik et al.	7,989,436	B2	8/2011	Hill et al.
7,135,190	B2	11/2006	Piao et al.	7,989,487	B2	8/2011	Welsh et al.
7,153,522	B1	12/2006	Ikeura et al.	8,022,053	B2	9/2011	Mueller et al.
7,163,681	B2	1/2007	Giles-Komar et al.	8,048,017	B2	11/2011	Xu
7,163,699	B2	1/2007	Besse	8,048,869	B2	11/2011	Bunschoten et al.
7,175,850	B2	2/2007	Cevc	8,063,030	B2	11/2011	Ellman
7,179,799	B2	2/2007	Hill et al.	8,071,576	B2	12/2011	Coelingh et al.
7,196,074	B2	3/2007	Blye et al.	8,071,729	B2	12/2011	Giles-Komar et al.
7,198,800	B1	4/2007	Ko	8,075,916	B2	12/2011	Song et al.
7,198,801	B2	4/2007	Carrara et al.	8,075,917	B2	12/2011	Chung et al.
7,226,910	B2	6/2007	Wilson et al.	8,076,317	B2	12/2011	Kulmann
7,247,625	B2	7/2007	Zhang et al.	8,076,319	B2	12/2011	Leonard
7,250,446	B2	7/2007	Sang Ita et al.	8,080,553	B2	12/2011	Keith et al.
7,267,829	B2	9/2007	Kirby et al.	8,088,605	B2	1/2012	Beaudet et al.
7,300,926	B2	11/2007	Prokai et al.	8,096,940	B2	1/2012	Josephson et al.
7,303,763	B2	12/2007	Ho	8,101,209	B2	1/2012	Legrand et al.
7,317,037	B2	1/2008	Fensome et al.	8,101,773	B2	1/2012	Smith et al.
7,329,654	B2	2/2008	Kanojia et al.	8,114,152	B2	2/2012	Furst
7,335,650	B2	2/2008	Potter et al.	8,114,434	B2	2/2012	Sasaki et al.
7,374,779	B2	5/2008	Chen et al.	8,114,442	B2	2/2012	Tucker et al.
7,378,404	B2	5/2008	Peters et al.	8,119,741	B2	2/2012	Pavlin
7,381,427	B2	6/2008	Ancira et al.	8,121,886	B2	2/2012	Azar
7,388,006	B2	6/2008	Schmees et al.	8,124,118	B2	2/2012	Lennernas et al.
7,387,789	B2	7/2008	Klose et al.	8,124,595	B2	2/2012	Boissonneault
7,414,043	B2	8/2008	Kosemund et al.	8,147,561	B2	4/2012	Binmoeller
7,427,413	B2	9/2008	Savoir et al.	8,148,546	B2	4/2012	Schuster et al.
7,427,609	B2	9/2008	Leonard	8,158,613	B2	4/2012	Staniforth et al.
7,429,576	B2	9/2008	Labrie	8,158,614	B2	4/2012	Lambert et al.
7,431,941	B2	10/2008	Besins et al.	8,163,722	B2	4/2012	Savoir et al.
7,456,159	B2	11/2008	Houze et al.	8,177,449	B2	5/2012	Bayly et al.
7,459,445	B2	12/2008	Hill et al.	8,182,833	B2	5/2012	Hermsmeyer
7,465,587	B2	12/2008	Imrich	8,187,615	B2	5/2012	Friedman
7,470,433	B2	12/2008	Carrara et al.	8,195,403	B2	6/2012	Ishikawa et al.
7,485,666	B2	2/2009	Villanueva et al.	8,202,736	B2	6/2012	Mous et al.
7,497,855	B2	3/2009	Ausiello et al.	8,217,024	B2	7/2012	Ahmed et al.
7,498,303	B2	3/2009	Arnold et al.	8,221,785	B2	7/2012	Chien
7,534,765	B2	5/2009	Gregg et al.	8,222,008	B2	7/2012	Thoene
7,534,780	B2	5/2009	Wyrwa et al.	8,222,237	B2	7/2012	Nickisch et al.
7,550,142	B2	6/2009	Giles-Komar et al.	8,227,454	B2	7/2012	Hill et al.
7,563,565	B1	7/2009	Matsuo et al.	8,227,509	B2	7/2012	Castro et al.
7,569,274	B2	8/2009	Besse et al.	8,241,664	B2	8/2012	Dudley et al.
7,572,779	B2	8/2009	Al08a et al.	8,247,393	B2	8/2012	Ahmed et al.
7,572,780	B2	8/2009	Hermsmeyer	8,257,724	B2	9/2012	Cromack et al.
7,589,082	B2	9/2009	Savoir et al.	8,257,725	B2	9/2012	Cromack et al.
7,671,027	B2	3/2010	Loumaye	8,268,352	B2	9/2012	Vaya et al.
7,674,783	B2	3/2010	Hermsmeyer	8,268,806	B2	9/2012	Labrie
7,687,281	B2	3/2010	Roth et al.	8,268,878	B2	9/2012	Armer et al.
7,687,485	B2	3/2010	Levinson et al.	8,273,730	B2	9/2012	Fernandez et al.
7,694,683	B2	4/2010	Callister et al.	8,287,888	B2	10/2012	Song et al.
7,704,983	B1	4/2010	Hodgen et al.	8,288,366	B2	10/2012	Chochinov et al.
7,727,720	B2	6/2010	Dhallan	8,318,898	B2	11/2012	Fasel et al.
7,732,408	B2	6/2010	Josephson et al.	8,324,193	B2	12/2012	Lee-Sepsick et al.
7,749,989	B2	7/2010	Hill et al.	8,329,680	B2	12/2012	Evans et al.
7,767,656	B2	8/2010	Shoichet et al.	8,337,814	B2	12/2012	Osbakken et al.
7,799,769	B2	9/2010	White et al.	8,344,007	B2	1/2013	Tang et al.
7,815,936	B2	10/2010	Hasenzahl et al.	8,349,820	B2	1/2013	Zeun et al.
7,815,949	B2	10/2010	Cohen	8,353,863	B2	1/2013	Imran
				8,357,723	B2	1/2013	Satyam
				8,361,995	B2	1/2013	Schramm
				8,362,091	B2	1/2013	Tamarkin et al.
				8,372,424	B2	2/2013	Berry et al.

US 10,639,375 B2

Page 5

(56)	References Cited				
U.S. PATENT DOCUMENTS					
8,372,806 B2	2/2013 Bohler et al.	2001/0031747 A1	10/2001	deZiegler et al.	
8,377,482 B2	2/2013 Laurie et al.	2001/0032125 A1	10/2001	Bhan et al.	
8,377,994 B2	2/2013 Gray et al.	2001/0034340 A1	10/2001	Pickar	
8,394,759 B2	3/2013 Barathur et al.	2001/0053383 A1	12/2001	Miranda et al.	
8,435,561 B2	3/2013 Besins et al.	2001/0056068 A1	12/2001	Chwalisz et al.	
8,415,332 B2	4/2013 Diliberi et al.	2002/0012710 A1	1/2002	Lansky	
8,420,111 B2	4/2013 Hermsmeyer	2002/0026158 A1	2/2002	Rathbone et al.	
8,435,972 B2	5/2013 Stein et al.	2002/0028788 A1	3/2002	Bunt et al.	
8,449,879 B2	5/2013 Laurent-Applegate et al.	2002/0035070 A1	3/2002	Gardlik et al.	
8,450,108 B2	5/2013 Boyce	2002/0058648 A1	5/2002	Hammerly	
8,454,945 B2	6/2013 McCook et al.	2002/0058926 A1	5/2002	Rathbone et al.	
8,455,468 B2	6/2013 Hoffman et al.	2002/0064541 A1	5/2002	Lapidot et al.	
8,461,138 B2	6/2013 Boissonault	2002/0076441 A1	6/2002	Shin et al.	
8,476,252 B2	7/2013 Achleitner et al.	2002/0102308 A1	8/2002	Wei et al.	
8,481,488 B2	7/2013 Carter	2002/0107230 A1	8/2002	Waldon et al.	
8,486,374 B2	7/2013 Tamarkin et al.	2002/0142017 A1	10/2002	Simonnet	
8,486,442 B2	7/2013 Matsushita et al.	2002/0151530 A1	10/2002	Leonard et al.	
8,492,368 B2	7/2013 Vanlandingham et al.	2002/0156394 A1	10/2002	Mehrotra et al.	
8,507,467 B2	8/2013 Matsui et al.	2002/0169150 A1	11/2002	Pickar	
8,512,693 B2	8/2013 Capito et al.	2002/0169205 A1	11/2002	Chwalisz et al.	
8,512,754 B2	8/2013 Needham	2002/0173510 A1	11/2002	Levinson et al.	
8,518,376 B2	8/2013 Tamarkin et al.	2002/0193356 A1	12/2002	Vanbeek et al.	
8,536,159 B2	9/2013 Li et al.	2002/0193758 A1	12/2002	Sandberg	
8,540,967 B2	9/2013 Barrett et al.	2002/0197286 A1	12/2002	Brandman et al.	
8,541,400 B2	9/2013 Johnsson et al.	2003/0003139 A1	1/2003	Lipp et al.	
8,551,462 B2	10/2013 Goldstein et al.	2003/0004145 A1	1/2003	Leonard	
8,557,281 B2	10/2013 Halliday et al.	2003/0007994 A1	1/2003	Bunt et al.	
8,568,374 B2	10/2013 De Graaff et al.	2003/0027772 A1	2/2003	Breton	
8,591,951 B2	11/2013 Kohn et al.	2003/0044453 A1	3/2003	Dittgen et al.	
8,613,951 B2	12/2013 Zale et al.	2003/0049307 A1	3/2003	Gyurik	
8,633,178 B2	1/2014 Bernick et al.	2003/0064097 A1	4/2003	Patel et al.	
8,633,180 B2	1/2014 Li et al.	2003/0064975 A1	4/2003	Koch et al.	
8,636,787 B2	1/2014 Sabaria	2003/0072760 A1	4/2003	Sirbasku	
8,636,982 B2	1/2014 Tamarkin et al.	2003/0073248 A1	4/2003	Roth et al.	
8,653,129 B2	2/2014 Fein et al.	2003/0073673 A1	4/2003	Hesch	
8,658,627 B2	2/2014 Voskuhl	2003/0077297 A1	4/2003	Chen et al.	
8,658,628 B2	2/2014 Baucom	2003/0078245 A1	4/2003	Bennink et al.	
8,663,681 B2	3/2014 Nakamichi et al.	2003/0091620 A1	5/2003	Fikstad et al.	
8,663,692 B2	3/2014 Mueller et al.	2003/0091640 A1	5/2003	Raman A Than et al.	
8,663,703 B2	3/2014 Lerner et al.	2003/0092691 A1	5/2003	Besse et al.	
8,664,207 B2	3/2014 Li et al.	2003/0096012 A1	5/2003	Besse et al.	
8,669,293 B2	3/2014 Levy et al.	2003/0104048 A1	6/2003	Patel et al.	
8,679,552 B2	3/2014 Guthery	2003/0109507 A1	6/2003	Franke et al.	
8,694,358 B2	4/2014 Tryfon	2003/0113268 A1	6/2003	Buenafae et al.	
8,697,127 B2	4/2014 Sah	2003/0114420 A1	6/2003	Salvati et al.	
8,697,710 B2	4/2014 Li et al.	2003/0114430 A1	6/2003	Macleod et al.	
8,703,105 B2	4/2014 Tamarkin et al.	2003/0124182 A1	7/2003	Shojaei et al.	
8,709,385 B2	4/2014 Tamarkin et al.	2003/0124191 A1	7/2003	Besse et al.	
8,709,451 B2	4/2014 Rapoport et al.	2003/0130558 A1	7/2003	Massara et al.	
8,715,735 B2	5/2014 Funke et al.	2003/0144258 A1	7/2003	Heil et al.	
8,721,331 B2	5/2014 Raghuprasad	2003/0157157 A1	8/2003	Luo et al.	
8,722,021 B2	5/2014 Friedman et al.	2003/0166509 A1	9/2003	Edwards et al.	
8,734,846 B2	5/2014 Ali et al.	2003/0170295 A1	9/2003	Kim et al.	
8,735,381 B2	5/2014 Podolski	2003/0175329 A1	9/2003	Azarnoff et al.	
8,741,336 B2	6/2014 Dipierro et al.	2003/0175333 A1	9/2003	Shefer et al.	
8,741,373 B2	6/2014 Bromley et al.	2003/0180352 A1	9/2003	Patel et al.	
8,753,661 B2	6/2014 Steinmuller et al.	2003/0181353 A1	9/2003	Nyce	
8,784,882 B2	7/2014 Mattern	2003/0181728 A1	9/2003	Salvati et al.	
8,815,261 B2	8/2014 Hanma	2003/0191096 A1	10/2003	Leonard et al.	
8,846,648 B2	9/2014 Bernick et al.	2003/0195177 A1	10/2003	Leonard et al.	
8,846,649 B2	9/2014 Bernick et al.	2003/0215496 A1	11/2003	Patel et al.	
8,933,059 B2	1/2015 Bernick et al.	2003/0219402 A1	11/2003	Rutter	
8,987,237 B2	3/2015 Bernick et al.	2003/0220297 A1	11/2003	Berstein et al.	
8,987,238 B2	3/2015 Bernick et al.	2003/0224057 A1	12/2003	Martin-Letellier et al.	
8,993,548 B2	3/2015 Bernick et al.	2003/0224059 A1	12/2003	Lerner et al.	
8,993,549 B2	3/2015 Bernick et al.	2003/0225047 A1	12/2003	Caubel et al.	
9,006,222 B2	4/2015 Bernick et al.	2003/0225048 A1	12/2003	Caubel et al.	
9,012,434 B2	4/2015 Bernick et al.	2003/0225050 A1	12/2003	Eichardi et al.	
9,289,382 B2	3/2016 Bernick et al.	2003/0228686 A1	12/2003	Klausner et al.	
2001/0005728 A1	6/2001 Guittard et al.	2003/0229057 A1	12/2003	Caubel et al.	
2001/0009673 A1	7/2001 Lipp et al.	2003/0235596 A1	12/2003	Gao et al.	
2001/0021816 A1	9/2001 Caillouetie	2003/0236236 A1	12/2003	Chen et al.	
2001/0023261 A1	9/2001 Ryoo et al.	2004/0009960 A1	1/2004	Heil et al.	
2001/0027189 A1	10/2001 Bennink et al.	2004/0022820 A1	2/2004	Anderson	
2001/0029357 A1	10/2001 Bunt et al.				

US 10,639,375 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2004/0034001 A1	2/2004	Karara	2005/0220825 A1	10/2005	Funke et al.
2004/0037881 A1	2/2004	Guittard et al.	2005/0220900 A1	10/2005	Popp et al.
2004/0039356 A1	2/2004	Maki et al.	2005/0222106 A1	10/2005	Bracht
2004/0043043 A1	3/2004	Schlyter et al.	2005/0228692 A1	10/2005	Hodgdon
2004/0043943 A1	3/2004	Guittard et al.	2005/0228718 A1	10/2005	Austin
2004/0044080 A1	3/2004	Place et al.	2005/0239747 A1	10/2005	Yang et al.
2004/0048900 A1	3/2004	Flood	2005/0239758 A1	10/2005	Roby
2004/0052824 A1	3/2004	AbouChakra-Vernet et al.	2005/0244360 A1	11/2005	Billoni
2004/0073024 A1	4/2004	Metcalf, III et al.	2005/0244522 A1	11/2005	Carrara et al.
2004/0077605 A1	4/2004	Salvati et al.	2005/0245902 A1	11/2005	Cornish et al.
2004/0077606 A1	4/2004	Salvati et al.	2005/0250746 A1	11/2005	Iammattieo
2004/0087548 A1	5/2004	Salvati et al.	2005/0250753 A1	11/2005	Cummings et al.
2004/0087564 A1	5/2004	Wright et al.	2005/0256028 A1	11/2005	Fink et al.
2004/0089308 A1	5/2004	Welch	2005/0266078 A1	12/2005	Yun et al.
2004/0092494 A9	5/2004	Dudley	2005/0271598 A1	12/2005	Jorda et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0272685 A1	12/2005	Hinrichs et al.
2004/0093261 A1	5/2004	Jain et al.	2005/0272712 A1	12/2005	Keith
2004/0097468 A1	5/2004	Wimalawansa	2006/0009428 A1	1/2006	Grubb et al.
2004/0101557 A1	5/2004	Gibson et al.	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0106542 A1	6/2004	Deaver et al.	2006/0018937 A1	1/2006	Friedman et al.
2004/0110732 A1	6/2004	Masini-Eteve et al.	2006/0019978 A1	1/2006	Balog
2004/0131670 A1	7/2004	Gao	2006/0020002 A1	1/2006	Salvati et al.
2004/0138103 A1	7/2004	Patt	2006/0030615 A1	2/2006	Fensome et al.
2004/0142012 A1	7/2004	Bunt et al.	2006/0034889 A1	2/2006	Jo et al.
2004/0146539 A1	7/2004	Gupta	2006/0034904 A1	2/2006	Weimann
2004/0146894 A1	7/2004	Warrington et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0161435 A1	8/2004	Gupta	2006/0052341 A1	3/2006	Cornish et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0069031 A1	3/2006	Loumaye
2004/0176336 A1	9/2004	Rodriguez	2006/0078618 A1	4/2006	Constantinides et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0083778 A1	4/2006	Allison et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0084704 A1	4/2006	Shih et al.
2004/0191276 A1	9/2004	Muni	2006/0088580 A1	4/2006	Meconi et al.
2004/0198706 A1	10/2004	Carrara et al.	2006/0089337 A1	4/2006	Casper et al.
2004/0210280 A1	10/2004	Liedtke	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0100180 A1	5/2006	Nubbemeyer et al.
2004/0219124 A1	11/2004	Gupta	2006/0106004 A1	5/2006	Brody et al.
2004/0225140 A1	11/2004	Fernandez et al.	2006/0110415 A1	5/2006	Gupta
2004/0234606 A1	11/2004	Levine et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0241219 A1	12/2004	Hille et al.	2006/0121102 A1	6/2006	Chiang
2004/0243437 A1	12/2004	Grace et al.	2006/0121626 A1	6/2006	Imrich
2004/0253319 A1	12/2004	Netke et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2004/0259817 A1	12/2004	Waldon et al.	2006/0135619 A1	6/2006	Kick et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0165744 A1	7/2006	Jamil et al.
2005/0003003 A1	1/2005	Basu et al.	2006/0193789 A1	8/2006	Tamarkin et al.
2005/0004088 A1	1/2005	Hesch	2006/0194775 A1	8/2006	Tofovic et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2006/0204557 A1	9/2006	Gupta et al.
2005/0014729 A1	1/2005	Pulaski	2006/0233743 A1	10/2006	Kelly
2005/0020550 A1	1/2005	Morris et al.	2006/0233841 A1	10/2006	Brodbeck et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2006/0235037 A1	10/2006	Purandare et al.
2005/0021009 A1	1/2005	Massara et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0025833 A1	2/2005	Aschkenasy et al.	2006/0246122 A1	11/2006	Langguth et al.
2005/0031651 A1	2/2005	Gervais et al.	2006/0247216 A1	11/2006	Haj-Yehia
2005/0042173 A1	2/2005	Besse et al.	2006/0247221 A1	11/2006	Coelingh Bennink et al.
2005/0042268 A1	2/2005	Aschkenasy et al.	2006/0251581 A1	11/2006	McIntyre et al.
2005/0048116 A1	3/2005	Straub et al.	2006/0252049 A1	11/2006	Shuler et al.
2005/0054991 A1	3/2005	Tobyn et al.	2006/0257472 A1	11/2006	Neilsen
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0275218 A1	12/2006	Tamarkin et al.
2005/0085453 A1	4/2005	Govindarajan	2006/0275360 A1	12/2006	Ahmed et al.
2005/0101579 A1	5/2005	Shippen	2006/0276414 A1	12/2006	Coelingh Bennink et al.
2005/0113350 A1	5/2005	Duesterberg et al.	2006/0280771 A1	12/2006	Groenewegen et al.
2005/0118244 A1	6/2005	Theobald et al.	2006/0280797 A1	12/2006	Shoichet et al.
2005/0118272 A1	6/2005	Besse et al.	2006/0280800 A1	12/2006	Nagi et al.
2005/0129756 A1	6/2005	Podhaisky et al.	2006/0292223 A1	12/2006	Woolfson et al.
2005/0152956 A1	7/2005	Dudley	2007/0004693 A1	1/2007	Woolfson et al.
2005/0153946 A1	7/2005	Hirsh et al.	2007/0004694 A1	1/2007	Woolfson et al.
2005/0164977 A1	7/2005	Coelingh Bennink	2007/0009559 A1	1/2007	Grubb et al.
2005/0182105 A1	8/2005	Nirschl et al.	2007/0010550 A1	1/2007	McKenzie
2005/0186141 A1	8/2005	Gonda et al.	2007/0014839 A1	1/2007	Bracht
2005/0187267 A1	8/2005	Hamann et al.	2007/0015698 A1	1/2007	Kleinman et al.
2005/0192253 A1	9/2005	Salvati et al.	2007/0021360 A1	1/2007	Nyce et al.
2005/0192310 A1	9/2005	Gavai et al.	2007/0027201 A1	2/2007	McComas et al.
2005/0196434 A1	9/2005	Briere	2007/0031491 A1	2/2007	Levine et al.
2005/0207990 A1	9/2005	Funke et al.	2007/0037780 A1	2/2007	Ebert et al.
2005/0209209 A1	9/2005	Koch et al.	2007/0037782 A1	2/2007	Hibino et al.
2005/0214384 A1	9/2005	Juturu et al.	2007/0042038 A1	2/2007	Besse

US 10,639,375 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2007/0060589 A1	3/2007	Purandare et al.	2008/0255089 A1	10/2008	Kat Am Reddy
2007/0066628 A1	3/2007	Zhang et al.	2008/0261931 A1	10/2008	Hedner et al.
2007/0066637 A1	3/2007	Zhang et al.	2008/0299220 A1	12/2008	Tamarkin et al.
2007/0066675 A1	3/2007	Zhang et al.	2008/0306036 A1	12/2008	Katamreddy
2007/0078091 A1	4/2007	Hubler et al.	2008/0312197 A1	12/2008	Rodriguez
2007/0088029 A1	4/2007	Balog et al.	2008/0312198 A1	12/2008	Rodriguez
2007/0093548 A1	4/2007	Diffendal et al.	2008/0319078 A1	12/2008	Katamreddy
2007/0116729 A1	5/2007	Palepu	2009/0004246 A1	1/2009	Woolfson et al.
2007/0116829 A1	5/2007	Prakash et al.	2009/0010968 A1	1/2009	Allart et al.
2007/0128263 A1	6/2007	Gargiulo et al.	2009/0011041 A1	1/2009	Musaeva et al.
2007/0154533 A1	7/2007	Dudley	2009/0017120 A1	1/2009	Trimble et al.
2007/0167418 A1	7/2007	Ferguson	2009/0022683 A1	1/2009	Song et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0053294 A1	2/2009	Prendergast
2007/0185068 A1	8/2007	Ferguson et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0190022 A1	8/2007	Bacopoulos et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0191319 A1	8/2007	Ke et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196415 A1	8/2007	Chen et al.	2009/0074859 A1	3/2009	Patel
2007/0196433 A1	8/2007	Ron et al.	2009/0081206 A1	3/2009	Leibovitz
2007/0207225 A1	9/2007	Squadrito	2009/0081278 A1	3/2009	De Graaff et al.
2007/0225281 A1	9/2007	Zhang et al.	2009/0081303 A1	3/2009	Savoir et al.
2007/0232574 A1	10/2007	Galey et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0093440 A1	4/2009	Murad
2007/0243229 A1	10/2007	Smith et al.	2009/0098069 A1	4/2009	Vacca
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0099106 A1	4/2009	Phiasivongsa et al.
2007/0254858 A1	11/2007	Cronk	2009/0099149 A1	4/2009	Liu et al.
2007/0255197 A1	11/2007	Humberstone et al.	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0264309 A1	11/2007	Chollet et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0264345 A1	11/2007	Eros et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0264349 A1	11/2007	Lee et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0286819 A1	12/2007	DeVries et al.	2009/0143344 A1	6/2009	Chang
2007/0287688 A1	12/2007	Chan et al.	2009/0164341 A1	6/2009	Sunvold et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0292359 A1	12/2007	Friedman et al.	2009/0181088 A1	7/2009	Song et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0186081 A1	7/2009	Holm et al.
2007/0292461 A1	12/2007	Tamarkin et al.	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0292493 A1	12/2007	Briere	2009/0203658 A1	8/2009	Marx et al.
2007/0298089 A1	12/2007	Saeki et al.	2009/0214474 A1	8/2009	Jennings
2008/0026035 A1	1/2008	Chollet et al.	2009/0227025 A1	9/2009	Nichols et al.
2008/0026040 A1	1/2008	Farr et al.	2009/0227550 A1	9/2009	Mattern
2008/0026062 A1	1/2008	Farr et al.	2009/0232897 A1	9/2009	Sahoo et al.
2008/0038219 A1	2/2008	Mosbaugh et al.	2009/0258096 A1	10/2009	Cohen
2008/0038350 A1	2/2008	Gerecke et al.	2009/0264395 A1	10/2009	Creasy
2008/0039405 A1	2/2008	Langley et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0050317 A1	2/2008	Tamarkin et al.	2009/0285772 A1	11/2009	Phiasivongsa et al.
2008/0051351 A1	2/2008	Ghisalberti	2009/0285869 A1	11/2009	Trimble
2008/0063607 A1	3/2008	Tamarkin et al.	2009/0318558 A1	12/2009	Kim et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2009/0324714 A1	12/2009	Liu et al.
2008/0069791 A1	3/2008	Beissert	2009/0325916 A1	12/2009	Zhang et al.
2008/0085877 A1	4/2008	Bortz	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0095831 A1	4/2008	Mc Graw	2010/0028360 A1	2/2010	Atwood
2008/0095838 A1	4/2008	Abou Chakra-Vernet	2010/0034838 A1	2/2010	Staniforth et al.
2008/0113953 A1	5/2008	De Vries et al.	2010/0034880 A1	2/2010	Sintov et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0040671 A1	2/2010	Ahmed et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0048523 A1	2/2010	Bachman et al.
2008/0125402 A1	5/2008	Dilberti	2010/0055138 A1	3/2010	Margulies et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0074959 A1	3/2010	Hansom et al.
2008/0138390 A1	6/2008	Hsu et al.	2010/0086501 A1	4/2010	Chang et al.
2008/0139392 A1	6/2008	Acosta-Zara et al.	2010/0086599 A1	4/2010	Huempel et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0092568 A1	4/2010	Lerner et al.
2008/0153789 A1	6/2008	Dmowski et al.	2010/0105071 A1	4/2010	Laufer et al.
2008/0175814 A1	7/2008	Phiasivongsa et al.	2010/0119585 A1	5/2010	Hille et al.
2008/0175905 A1	7/2008	Liu et al.	2010/0129320 A1	5/2010	Phiasivongsa et al.
2008/0175908 A1	7/2008	Liu et al.	2010/0136105 A1	6/2010	Chen et al.
2008/0188829 A1	8/2008	Creasy	2010/0137265 A1	6/2010	Leonard
2008/0206156 A1	8/2008	Cronk	2010/0137271 A1	6/2010	Chen et al.
2008/0206159 A1	8/2008	Tamarkin et al.	2010/0143420 A1	6/2010	Shenoy et al.
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0143481 A1	6/2010	Shenoy et al.
2008/0214512 A1	9/2008	Seitz et al.	2010/0150993 A1	6/2010	Theobald et al.
2008/0220069 A1	9/2008	Allison	2010/0152144 A1	6/2010	Hermsmeyer
2008/0226698 A1	9/2008	Tang et al.	2010/0168228 A1	7/2010	Bose et al.
2008/0227763 A1	9/2008	Lanquetin et al.	2010/0183723 A1	7/2010	Laurent-Applegate et al.
2008/0234199 A1	9/2008	Kat Am Reddy	2010/0184736 A1	7/2010	Coelingh Bennink et al.
2008/0234240 A1	9/2008	Duesterberg et al.	2010/0190758 A1	7/2010	Fauser et al.
2008/0255078 A1	10/2008	Kat Am Reddy	2010/0204326 A1	8/2010	D'Souza

US 10,639,375 B2

Page 8

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2010/0247482 A1	9/2010	Cui et al.	2012/0065221 A1	3/2012	Babul	
2010/0247632 A1	9/2010	Dong et al.	2012/0087872 A1	4/2012	Tamarkin et al.	
2010/0247635 A1	9/2010	Rosenberg et al.	2012/0101073 A1	4/2012	Mannion et al.	
2010/0255085 A1	10/2010	Liu et al.	2012/0121517 A1	5/2012	Song et al.	
2010/0273730 A1	10/2010	Hsu et al.	2012/0121692 A1	5/2012	Xu et al.	
2010/0278759 A1	11/2010	Murad	2012/0122829 A1	5/2012	Taravella et al.	
2010/0279988 A1	11/2010	Setiawan et al.	2012/0128625 A1	5/2012	Shalwitz et al.	
2010/0291191 A1	11/2010	Shoichet et al.	2012/0128654 A1	5/2012	Terpstra et al.	
2010/0292199 A1	11/2010	Leverb et al.	2012/0128683 A1	5/2012	Shantha	
2010/0303825 A9	12/2010	Sirbasku	2012/0128733 A1	5/2012	Perrin et al.	
2010/0312137 A1	12/2010	Gilmour et al.	2012/0128777 A1	5/2012	Keck et al.	
2010/0316724 A1	12/2010	Whitfield et al.	2012/0129773 A1	5/2012	Geier et al.	
2010/0322884 A1	12/2010	Dipietro et al.	2012/0129819 A1	5/2012	Vancaillie et al.	
2010/0330168 A1	12/2010	Gicquel et al.	2012/0136013 A1	5/2012	Li et al.	
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0142645 A1	6/2012	Marx	
2011/0039814 A1	2/2011	Huatan et al.	2012/0148670 A1	6/2012	Kim et al.	
2011/0053845 A1	3/2011	Levine et al.	2012/0149748 A1	6/2012	Shanler et al.	
2011/0066473 A1	3/2011	Bernick et al.	2012/0172343 A1	7/2012	Lindenthal et al.	
2011/0076775 A1	3/2011	Stewart et al.	2012/0184515 A1	7/2012	Klar et al.	
2011/0076776 A1	3/2011	Stewart et al.	2012/0231052 A1	9/2012	Sitruk-Ware et al.	
2011/0086825 A1	4/2011	Chatroux	2012/0232011 A1	9/2012	Kneissel et al.	
2011/0087192 A1	4/2011	Uhland et al.	2012/0232042 A1	9/2012	Klar et al.	
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0263679 A1	10/2012	Marlow et al.	
2011/0098258 A1	4/2011	Masini-Eteve et al.	2012/0269721 A1	10/2012	Weng et al.	
2011/0098631 A1	4/2011	McIntyre et al.	2012/0269878 A2	10/2012	Cantor et al.	
2011/0104268 A1	5/2011	Pachot et al.	2012/0277249 A1	11/2012	Andersson et al.	
2011/0104289 A1	5/2011	Sa Voir Vilboeuf et al.	2012/0277727 A1	11/2012	Doshi et al.	
2011/0130372 A1	6/2011	Agostinacchio et al.	2012/0283671 A1	11/2012	Shibata et al.	
2011/0135719 A1	6/2011	Besins	2012/0295911 A1	11/2012	Mannion et al.	
2011/0142945 A1	6/2011	Chen et al.	2012/0301517 A1	11/2012	Zhang et al.	
2011/0152840 A1	6/2011	Lee et al.	2012/0301538 A1	11/2012	Gordon-Beresford et al.	
2011/0158920 A1	6/2011	Morley et al.	2012/0302535 A1	11/2012	Caufriez et al.	
2011/0171140 A1	7/2011	Illum et al.	2012/0316130 A1	12/2012	Hendrix	
2011/0182997 A1	7/2011	Lewis et al.	2012/0316496 A1	12/2012	Hoffmann et al.	
2011/0190201 A1	8/2011	Hyde et al.	2012/0321579 A1	12/2012	Edelson et al.	
2011/0195031 A1	8/2011	Du	2012/0322779 A9	12/2012	Voskuhl	
2011/0195114 A1	8/2011	Carrara et al.	2012/0328549 A1	12/2012	Edelson et al.	
2011/0195944 A1	8/2011	Mura et al.	2012/0329738 A1	12/2012	Liu	
2011/0217341 A1	9/2011	Sah	2013/0004619 A1	1/2013	Chow et al.	
2011/0238003 A1	9/2011	Bruno-Raimondi et al.	2013/0011342 A1	1/2013	Tamarkin et al.	
2011/0244043 A1	10/2011	Xu et al.	2013/0017239 A1	1/2013	Viladot Petit et al.	
2011/0250256 A1	10/2011	Hyun-Oh et al.	2013/0022674 A1	1/2013	Dudley et al.	
2011/0250259 A1	10/2011	Buckman	2013/0023505 A1	1/2013	Garfield et al.	
2011/0250274 A1	10/2011	Shaked et al.	2013/0023823 A1	1/2013	Simpson et al.	
2011/0256092 A1	10/2011	Phiasivongsa et al.	2013/0028850 A1	1/2013	Tamarkin et al.	
2011/0262373 A1	10/2011	Umbert Millet	2013/0029947 A1	1/2013	Nachaegari et al.	
2011/0262494 A1	10/2011	Achleitner et al.	2013/0029957 A1	1/2013	Giliyar et al.	
2011/0268665 A1	11/2011	Tamarkin et al.	2013/0045266 A1	2/2013	Choi et al.	
2011/0275584 A1	11/2011	Wilckens et al.	2013/0045953 A1	2/2013	Sitruk-Ware et al.	
2011/0281832 A1	11/2011	Li et al.	2013/0059795 A1	3/2013	Lo et al.	
2011/0287094 A1	11/2011	Penthasi et al.	2013/0064897 A1	3/2013	Binay	
2011/0293720 A1	12/2011	General et al.	2013/0072466 A1	3/2013	Choi et al.	
2011/0294738 A1	12/2011	Ren et al.	2013/0084257 A1	4/2013	Ishida et al.	
2011/0300167 A1	12/2011	McMurry et al.	2013/0116215 A1	5/2013	Coma et al.	
2011/0301087 A1	12/2011	McBride et al.	2013/0116222 A1	5/2013	Arnold et al.	
2011/0306579 A1	12/2011	Stein	2013/0122051 A1	5/2013	Abidi et al.	
2011/0311592 A1	12/2011	Birbara	2013/0123175 A1	5/2013	Hill et al.	
2011/0312928 A1	12/2011	Nachaegari et al.	2013/0123220 A1	5/2013	Queiroz	
2011/0318405 A1	12/2011	Erwin	2013/0123351 A1	5/2013	Dewitt	
2011/0318431 A1	12/2011	Gulati	2013/0129818 A1	5/2013	Bernick et al.	
2012/0009276 A1	1/2012	DeGroote	2013/0131027 A1	5/2013	Pakkalin et al.	
2012/0015350 A1	1/2012	Nabatianyan et al.	2013/0131028 A1	5/2013	Snyder et al.	
2012/0021041 A1	1/2012	Rossi et al.	2013/0131029 A1	5/2013	Bakker et al.	
2012/0028888 A1	2/2012	Janz et al.	2013/0149314 A1	6/2013	Bullerdiek et al.	
2012/0028910 A1	2/2012	Combal et al.	2013/0164225 A1	6/2013	Tamarkin et al.	
2012/0028936 A1	2/2012	Gloge et al.	2013/0164346 A1	6/2013	Lee et al.	
2012/0045532 A1	2/2012	Cohen	2013/0165744 A1	6/2013	Carson et al.	
2012/0046264 A1	2/2012	Simes et al.	2013/0178452 A1	7/2013	King	
2012/0046518 A1	2/2012	Yoakum et al.	2013/0183254 A1	7/2013	Zhou et al.	
2012/0052077 A1	3/2012	Truitt, III et al.	2013/0183325 A1	7/2013	Bottoni et al.	
2012/0058171 A1	3/2012	De Graaff et al.	2013/0189193 A1	7/2013	Tamarkin et al.	
2012/0058962 A1	3/2012	Cumming et al.	2013/0189196 A1	7/2013	Tamarkin et al.	
2012/0058979 A1	3/2012	Keith et al.	2013/0189230 A1	7/2013	Shoichet et al.	
2012/0064135 A1	3/2012	Levin et al.	2013/0189368 A1	7/2013	Mosqueira et al.	
2012/0065179 A1	3/2012	Andersson				

US 10,639,375 B2

Page 9

(56)

References Cited**FOREIGN PATENT DOCUMENTS****U.S. PATENT DOCUMENTS**

2013/0210709 A1	8/2013	McMurtry et al.
2013/0216550 A1	8/2013	Penninger et al.
2013/0216596 A1	8/2013	Viladot Petit et al.
2013/0224177 A1	8/2013	Kim et al.
2013/0224257 A1	8/2013	Sah et al.
2013/0224268 A1	8/2013	Alam et al.
2013/0224300 A1	8/2013	Maggio
2013/0225412 A1	8/2013	Sardari Lodriche et al.
2013/0225542 A1	8/2013	Poegh et al.
2013/0226113 A1	8/2013	Schumacher et al.
2013/0243696 A1	9/2013	Wang et al.
2013/0245253 A1	9/2013	Marx et al.
2013/0245570 A1	9/2013	Jackson
2013/0261096 A1	10/2013	Merian et al.
2013/0266645 A1	10/2013	Becker et al.
2013/0267485 A1	10/2013	Da Silva Maia Filho
2013/0273167 A1	10/2013	Lee et al.
2013/0274211 A1	10/2013	Burman et al.
2013/0280213 A1	10/2013	Voskuhl
2013/0316374 A1	11/2013	Penninger et al.
2013/0317065 A1	11/2013	Tatani et al.
2013/0317315 A1	11/2013	Lu et al.
2013/0324565 A1	12/2013	Li et al.
2013/0331363 A1	12/2013	Li et al.
2013/0338122 A1	12/2013	Bernick et al.
2013/0338123 A1	12/2013	Bernick et al.
2013/0338124 A1	12/2013	Li et al.
2013/0345187 A1	12/2013	Rodriguez Oquendo
2014/0018335 A1	1/2014	Tatani et al.
2014/0024590 A1	1/2014	Weidhaas et al.
2014/0031289 A1	1/2014	Song et al.
2014/0031323 A1	1/2014	Perez
2014/0066416 A1	3/2014	Leunis et al.
2014/0072531 A1	3/2014	Kim et al.
2014/0079686 A1	3/2014	Barman et al.
2014/0088051 A1	3/2014	Bernick et al.
2014/0088058 A1	3/2014	Maurizio
2014/0088059 A1	3/2014	Perumal et al.
2014/0094426 A1	4/2014	Drummond et al.
2014/0094440 A1	4/2014	Bernick et al.
2014/0094441 A1	4/2014	Bernick et al.
2014/0099362 A1	4/2014	Bernick et al.
2014/0100159 A1	4/2014	Conrad
2014/0100204 A1	4/2014	Bernick et al.
2014/0100205 A1	4/2014	Bernick et al.
2014/0100206 A1	4/2014	Bernick et al.
2014/0113889 A1	4/2014	Connor et al.
2014/0127185 A1	5/2014	Stein et al.
2014/0127280 A1	5/2014	Duesterberg et al.
2014/0127308 A1	5/2014	Opara et al.
2014/0128798 A1	5/2014	Janson et al.
2014/0148491 A1	5/2014	Valia et al.
2014/0186332 A1	7/2014	Ezrin et al.
2014/0187487 A1	7/2014	Shoichet et al.
2014/0193523 A1	7/2014	Henry
2014/0194396 A1	7/2014	Li et al.
2014/0206616 A1	7/2014	Ko et al.
2014/0213565 A1	7/2014	Bernick et al.
2014/0288035 A1	9/2014	Hubner et al.
2014/0329783 A1	11/2014	Bernick et al.
2014/0335193 A1	11/2014	Rintoul et al.
2014/0370084 A1	12/2014	Bernick et al.
2014/0371182 A1	12/2014	Bernick et al.
2014/0371183 A1	12/2014	Bernick et al.
2014/0371184 A1	12/2014	Bernick et al.
2014/0371185 A1	12/2014	Bernick et al.
2015/0031654 A1	1/2015	Amadio
2015/0045335 A1	2/2015	Bernick et al.
2015/0133421 A1	5/2015	Bernick et al.
2015/0196640 A1	7/2015	Cacace et al.
2015/0202211 A1	7/2015	Amadio et al.
2017/0340739 A1	11/2017	Cacace et al.

CA	2856520	A1	5/2013
CN	102258455		11/2011
CN	102258455	A	11/2011
EP	0275716	A1	7/1988
EP	0622075	A1	2/1994
EP	0622075	A1	11/1994
EP	0785211	A1	1/1996
EP	0785212	A1	1/1996
EP	0811381		6/1997
EP	0785211	A1	7/1997
EP	0785212	A1	7/1997
EP	0811381	B1	5/2003
EP	1094781	B1	7/2006
EP	2191833		6/2010
EP	2191833	B1	2/2013
GB	452238	A	8/1936
GB	720561		12/1954
GB	720561	A	12/1954
GB	848881	A	9/1960
GB	874368		8/1961
GB	874368	A	8/1961
GB	1589946	A	5/1981
IN	216026		3/2008
IN	2005K000053		9/2009
IN	244217		11/2010
JP	2007-516259	A	6/2007
JP	2009-510127	A	3/2009
MX	2014/006256	A	10/2014
WO	WO-1990011064	A1	10/1990
WO	WO-1993017686	A1	9/1993
WO	WO-1994022426	A1	3/1994
WO	WO-1995030409	A1	11/1995
WO	WO-1996009826	A2	4/1996
WO	WO-9619975	A1	7/1996
WO	WO-1996030000	A1	10/1996
WO	WO-9705491		2/1997
WO	WO-1997043989	A1	11/1997
WO	WO-1998010293	A1	3/1998
WO	WO-1998032465	A1	7/1998
WO	WO-1998051280	A1	11/1998
WO	WO-1999039700	A1	2/1999
WO	WO-1999032072	A1	7/1999
WO	WO-9939700	A1	8/1999
WO	WO-1999042109	A1	8/1999
WO	WO-9943304		9/1999
WO	WO-1999048477	A1	9/1999
WO	WO-1999053910	A2	10/1999
WO	WO-1999063974	A2	12/1999
WO	WO-2000001351	A1	1/2000
WO	WO-2000006175	A1	2/2000
WO	WO-2000045795	A2	8/2000
WO	WO-2000050007	A1	8/2000
WO	WO-2000059577	A1	10/2000
WO	WO-2000038659	A1	11/2000
WO	WO-2001037808	A1	11/2000
WO	WO-2000076522	A1	12/2000
WO	WO-2002007700	A2	7/2001
WO	WO-2001054699	A1	8/2001
WO	WO-2001060325	A1	8/2001
WO	WO-2002011768	A1	2/2002
WO	WO-2002022132	A2	3/2002
WO	WO-0241878	A2	5/2002
WO	WO-2002040008	A1	5/2002
WO	WO-2002053131	A1	7/2002
WO	WO-2002078602	A3	2/2003
WO	WO-03028667	A2	4/2003
WO	WO-2003041718	A1	5/2003
WO	WO-2003041741	A1	5/2003
WO	WO-2003068186	A1	8/2003
WO	WO-2003077923	A1	9/2003
WO	WO-2003082254	A1	10/2003
WO	WO-2002078604	A3	11/2003
WO	WO-2003092588	A2	11/2003
WO	WO-2004014397	A1	2/2004
WO	WO-2004014432	A1	2/2004
WO	WO-2004017983	A1	3/2004
WO	WO-2005027911	A1	3/2004

US 10,639,375 B2

Page 10

(56)	References Cited							
FOREIGN PATENT DOCUMENTS								
WO	WO-2004032897	A2	4/2004	WO	WO-2013045404	A2		
WO	WO-2004052336	A2	6/2004	WO	WO-2013059285	A1		
WO	WO-2005120517	A1	6/2004	WO	WO-2013063279	A1		
WO	WO-2004054540	A2	7/2004	WO	WO-2013064620	A1		
WO	WO-2004080413	A2	9/2004	WO	WO-2013071281	A1		
WO	WO-2005030175	A1	4/2005	WO	WO-2013078422	A2		
WO	WO-2005081825	A2	9/2005	WO	WO-2013088254	A1		
WO	WO-2005087194	A1	9/2005	WO	WO-2013102665	A1		
WO	WO-2005087199	A2	9/2005	WO	WO-2013106437	A1		
WO	WO-2005105059	A1	11/2005	WO	WO-2013113690	A1		
WO	WO-2005115335	A1	12/2005	WO	WO-2013124415	A1		
WO	WO-2005120470	A1	12/2005	WO	WO-2013127727	A1		
WO	WO-2005120517	A1	12/2005	WO	WO-2013127728	A1		
WO	WO-2006013369	A2	2/2006	WO	WO-2013144356	A1		
WO	WO-2006034090	A1	3/2006	WO	WO-2013149258	A2		
WO	WO-2006036899	A2	4/2006	WO	WO-2013158454	A2		
WO	WO-2006053172	A2	5/2006	WO	WO-2013170052	A1		
WO	WO-2006105615	A1	10/2006	WO	WO-2013178587	A1		
WO	WO-2006113505	A2	10/2006	WO	WO-2013181449	A1		
WO	WO-2006138686	A1	12/2006	WO	WO-2013192248	A1		
WO	WO-2006138735	A2	12/2006	WO	WO-2013192249	A1		
WO	WO-2007038796	A1	4/2007	WO	WO-2013192250	A1		
WO	WO-2007045027	A1	4/2007	WO	WO-2013192251	A1		
WO	WO-2007103294	A2	9/2007	WO	WO-2014001904	A1		
WO	WO-2006138735	A3	10/2007	WO	WO-2014004424	A1		
WO	WO-2007120868	A2	10/2007	WO	WO-2014009434	A1		
WO	WO-007124250	A2	11/2007	WO	WO-2014018569	A1		
WO	WO-2007123790	A1	11/2007	WO	WO-2014018570	A1		
WO	WO-007144151	A1	12/2007	WO	WO-2014018571	A2		
WO	WO-2006138686	A1	12/2007	WO	WO-2014018856	A1		
WO	WO-2007124250	A3	12/2007	WO	WO-2014018932	A2		
WO	WO-2007144151	A1	12/2007	WO	WO-2014031958	A1		
WO	WO-2007103294	A3	4/2008	WO	WO-2014041120	A1		
WO	WO-2008049516	A3	5/2008	WO	WO-2014052792	A1		
WO	WO-2008049516	A3	6/2008	WO	WO-2014056897	A1		
WO	WO-2008152444	A2	12/2008	WO	WO-2014066442	A2		
WO	WO-2009002542	A1	12/2008	WO	WO-2014074846	A1		
WO	WO-2009036311	A1	3/2009	WO	WO-2014076231	A1		
WO	WO-2009040818		4/2009	WO	WO-2014076569	A2		
WO	WO-2008152444	A3	6/2009	WO	WO-2014081598	A1		
WO	WO-2009069006	A2	6/2009	WO	WO-2014086739	A1		
WO	WO-2009098072	A2	8/2009	WO	WO-2014093114	A1		
WO	WO-2009098072	A3	10/2009	WO	WO-2014104784	A1		
WO	WO-2009133352	A2	11/2009	OTHER PUBLICATIONS				
WO	WO-2009069006	A3	12/2009	Abbas, M.A., et al., "Regression of Endometrial Implants Treated with Vitamin D3 in a Rat Model of Endometriosis," European Journal of Pharmacology 715(1-3):72-75, Elsevier Science, Netherlands (2013).				
WO	WO-2010033188	A2	3/2010	Abitec Corporation Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2 pages (2013).				
WO	WO-2009133352	A3	10/2010	Advisory Action dated Jan. 29, 2007 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.				
WO	WO-2010146872	A1	12/2010	Alvarez, P., et al., "Ectopic Uterine Tissue as a Chronic Pain Generator," Neuroscience 225:269-282, Elsevier Science, United States (2012).				
WO	WO-2011000210	A1	1/2011	Application Note JASCO CD Spectra of Pharmaceuticals Substances Steroids, 2 pages.				
WO	WO-2011073995	A2	6/2011	Archer, D.F., et al., "Effects of Ospemifene on the Female Reproductive and Urinary Tracts : Translation From Preclinical Models into Clinical Evidence," Menopause, Lippincott-Raven Publishers, United States (2014).				
WO	WO-2011073995	A3	8/2011	Archer, F., et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study 9(1):21-31, (1992).				
WO	WO-2011120084	A1	10/2011	Ashburn, A.D., et al., "Cardiovascular , Hepatic and Renal Lesions in Mice Receiving Cortisone , Estrone and Progesterone," The Yale Journal of Biology and Medicine 35:329-340, Yale Journal of Biology and Medicine, United States (1963).				
WO	WO-2011128336	A1	10/2011	Bartosova, L. and Bajgar, J., "Transdermal Drug Delivery in Vitro Using Diffusion Cells," Current Medicinal Chemistry 19(27):4671-4677, Bentham Science Publishers, Netherlands (2012).				
WO	WO-2010033188	A3	11/2011	Benbow, A.L. and Waddell, B.J., "Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus During Rat Pregnancy," Biology of Reproduction 52(6):1327-1333, Society for the Study of Reproduction, United States (1995).				
WO	WO-2012009778	A2	1/2012					
WO	WO-2012024361	A1	2/2012					
WO	WO-2012055814	A1	5/2012					
WO	WO-2012055840	A1	5/2012					
WO	WO-2012065740	A1	5/2012					
WO	WO-2012098090	A1	7/2012					
WO	WO-2012116277	A1	8/2012					
WO	WO-2012118563	A2	9/2012					
WO	WO-2012120365	A1	9/2012					
WO	WO-2012127501	A2	9/2012					
WO	WO-2012156561	A1	11/2012					
WO	WO-2012156822	A1	11/2012					
WO	WO-2012158483	A2	11/2012					
WO	WO-2012166909	A1	12/2012					
WO	WO-2012170578	A1	12/2012					
WO	WO-2013011501	A1	1/2013					
WO	WO-20122009778	A3	2/2013					
WO	WO-2013025449	A1	2/2013					
WO	WO-2013028639	A1	2/2013					
WO	WO-2013035101	A1	3/2013					
WO	WO-2013044067	A1	3/2013					

US 10,639,375 B2

Page 11

(56)

References Cited

OTHER PUBLICATIONS

- Blake, E.J., et al., "Single and Multidose Pharmacokinetic Study of a Vaginal Micronized Progesterone insert (Endometrin) Compared with Vaginal Gel in Healthy Reproductive-Aged Female Subjects," *Fertility and Sterility* 94(4):1296-1301, Elsevier for the American Society for Reproductive Medicine, United States (2010).
- Brader Christensson, J., et al., "Positive Patch Test Reactions to Oxidized Limonene: Exposure and Relevance," *Contact Dermatitis* 71(5):264-272, Wiley, England (2014).
- Christen, R.D., et al., "Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin," *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 11(12):2417-2426, American Society of Clinical Oncology, United States (1993).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Differ in Allergenic Activity," *Contact Dermatitis* 59(6):344-352, Wiley, England (2008).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Show Specific Patch Test Reactions," *Contact Dermatitis* 70(5):291-299, Wiley, England (2014).
- Cincinelli, E., et al., "Direct Transport of Progesterone From Vagina to Uterus," *Obstetrics and Gynecology* 95(3):403-406, Lippincott Williams & Wilkins, United States (2000).
- Corbett, S.H., et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina : Focus on Vulvodynia," *Southern Medical Journal* 107(7):433-436, Southern Medical Association, United States (2014).
- Crutchley, H.O., et al., "Estrogen Receptor Beta, but Not Estrogen Receptor Alpha, Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium," *The Journal of Clinical Endocrinology and Metabolism* 86(3):1370-1378, Endocrine Society, United States (2001).
- Diramio, J.A., et al., "Poly(Ethylene Glycol) Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," Masters of Science Thesis, University of Georgia, Athens, Georgia, 131 pages (2002).
- Engelhardt, H., et al., "Conceptus influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy," *Biology of Reproduction* 66(6):1875-1880, Society for the Study of Reproduction, United States (2002).
- Ettinger, B., et al., "Comparison of Endometrial Growth Produced by Unopposed Conjugated Estrogens or by Micronized Estradiol in Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 176(1 Pt1):112-117, Elsevier, United States (1997).
- Excipients for Pharmaceuticals, SASOL Olefins & Surfactants GmbH, 28 pages (2010).
- Filipsson, F., et al., "Concise International Chemical Assessment Document 5," Limonene, first draft, World Health Organization, Geneva, 36 pages (1998).
- Final Office Action dated Oct. 26, 2012 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Flyvholm, M.A. and Menne, T., "Sensitizing Risk of butylated Hydroxytoluene Based on Exposure and Effect Data," *Contact Dermatitis* 23(5):341-345, Wiley, England (1990).
- Franklin, R.D. and Kutteh, W.H., "Characterization of Immunoglobulins and Cytokines in Human Cervical Mucus : influence of Exogenous and Endogenous Hormones," *Journal of Reproductive Immunology* 42(2):93-106, Elsevier/North-Holland Biomedical Press, Ireland (1999).
- Franz, T.J., et al., "Use of Excised Human Skin to Assess the Bioequivalence of Topical Products," *Skin Pharmacology and Physiology* 22(5):276-286, Karger, Switzerland (2009).
- Fuchs, K.O., et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Cutis* 71(6):481-488, Frontline Medical Communications, United States (2003).
- Furness, S., et al., "Hormone therapy in Postmenopausal Women and Risk of Endometrial Hyperplasia," *The Cochrane Database of Systematic Reviews* 8:1-204, Wiley, England (2012).
- Gafvert, E., et al., "Free Radicals in Antigen formation: Reduction of Contact Allergic Response to Hydroperoxides by Epidermal Treatment with Antioxidants," *The British Journal of Dermatology* 146(4):649-656, Blackwell Scientific Publications, England (2002).
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 6 pages (2012).
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 5 pages (2012).
- Gattefossé, "Excipients for Safe and Effective Topical Delivery," <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#> (2012).
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 8 pages 2012.
- Gillet, J.Y., et al., "Induction of Amenorrhea During Hormone Replacement therapy : Optimal Micronized Progesterone Dose A Multicenter Study," *Maturitas* 19(2):103-115, Elsevier/North Holland Biomedical Press, Ireland (1994).
- Glaser, R.L., et al., "Pilot Study : Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina," *Gynecologic and Obstetric Investigation* 66(2):111-118, Basel, New York, Karger, Switzerland (2008).
- Golatowski, C., et al., "Comparative Evaluation of Saliva Collection Methods for Proteome Analysis," *International Journal of Clinical Chemistry* 419:42-46, Elsevier, Netherlands (2013).
- Graham, J.D. and Clarke, C.L., "Physiological Action of Progesterone in Target Tissues," *Endocrine Reviews* 18(4):502-519, Endocrine Society, United States (1997).
- Groothuis, P.G., et al., "Estrogen and the Endometrium : Lessons Learned From Gene Expression Profiling in Rodents and Human," *Human Reproduction Update* 13(4):405-417, Published for the European Society of Human Reproduction and Embryology by Oxford University Press, England (2007).
- Hamid, K.A., et al., "the Effects of Common Solubilizing Agents on the intestinal Membrane Barrier Functions and Membrane Toxicity in Rats," *International Journal of Pharmaceutics* 379(1):100-108, Amsterdam, Elsevier/North-Holland Biomedical Press, Netherlands (2009).
- Hatton, J., et al., "Safety and Efficacy of a Lipid Emulsion Containing Medium-Chain Triglycerides," *Clinical Pharmacy* 9(5):366-371, American Society of Hospital Pharmacists, United States (1990).
- He, F., et al., "Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia induced by Ovariectomy Combined with Estrogen," *Gynecologic and Obstetric Investigation* 76(1):51-56, Karger, Switzerland (2013).
- Helmy, A., et al., "Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats," *Clinical Pharmacology & Biopharmaceutics*, S2, 7 pages (2014).
- Hostynk, J., et al., "Predicting absorption of fragrance chemicals through human skin," *Journal of the Society of Cosmetic Chemists* 46:221-229, (1995).
- Hurn, P.D. and Macrae, I.M., "Estrogen as a Neuroprotectant in Stroke," *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism* 20(4):631-652, Nature Publishing Group, United States (2000).
- Hyder, S.M., et al., "Synthetic Estrogen 17Alpha-Ethynodiol induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17Beta-Estradiol," *The Journal of Pharmacology and Experimental Therapeutics* 290(2):740-747, American Society for Pharmacology and Experimental Therapeutics, United States (1999).
- Joshi, S.G., et al., "Detection and Synthesis of a Progestagen-Dependent Protein in Human Endometrium," *Journal of Reproduction and Fertility* 59(2):273-285, Portland Press, England (1980).
- Kanno, J., et al., "The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses : Phase 1," *Environmental Health Perspectives* 109(8):785-794, N. C. National Institute of Environmental Health Sciences, United States (2001).
- Karlberg, A.T., et al., "Air Oxidation of D-Limonene (the Citrus Solvent) Creates Potent Allergens," *Contact Dermatitis* 26(5):332-340, Wiley, England (1992).

US 10,639,375 B2

Page 12

(56)

References Cited**OTHER PUBLICATIONS**

- Karlberg, A.T., et al., "Influence of an Anti-Oxidant on the formation of Allergenic Compounds During Auto-Oxidation of D-Limonene," *The Annals of Occupational Hygiene* 38(2):199-207, Oxford University Press, England (1994).
- Kaunitz, A.M. "Extended Duration Use of Menopausal Hormone therapy," *Menopause* 21(6):679-681, Lippincott-Raven Publishers, United States (2014).
- Kharode, Y., et al., "The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention," *Endocrinology* 149(12):6084-6091, Endocrine Society, United States (2008).
- Kim, Y.W., et al., "Safety Evaluation and Risk Assessment of D-Limonene," *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 16(1):17-38, Informa Healthcare, England (2013).
- Koga, K., et al., "Enhancing Mechanism of Labrasol on intestinal Membrane Permeability of the Hydrophilic Drug Gentamicin Sulfate," *European Journal of Pharmaceutics and Biopharmaceutics : Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik E.V* 64(1):82-91, Elsevier Science, Netherlands (2006).
- Komm, B.S., et al., "Bazedoxifene Acetate : A Selective Estrogen Receptor Modulator with Improved Selectivity," *Endocrinology* 146(9):3999-4008, Endocrine Society, United States (2005).
- Kumasaka, T., et al., "Effects of Various forms of Progestin on the Endometrium of the Estrogen-Primed, Ovariectomized Rat," *Endocrine Journal* 41(2):161-169, Japan Endocrine Society, Japan (1994).
- Kuon, R.J. and Garfield, R.E., "Actions of Progestins for the inhibition of Cervical Ripening and Uterine Contractions to Prevent Preterm Birth," *Facts, Views & Vision in Obgyn* 4(2):110-119, Flemish Society of Obstetrics & Gynaecology, Belgium (2012).
- Kuon, R.J., et al., "A Novel Optical Method to Assess Cervical Changes During Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor," *American Journal of Obstetrics and Gynecology* 205(1):e15-82.e20, Elsevier, United States (2011).
- Kuon, R.J., et al., "Pharmacologic Actions of Progestins to inhibit Cervical Ripening and Prevent Delivery Depend on their Properties , the Route of Administration , and the Vehicle," *American Journal of Obstetrics and Gynecology* 202(5):455.e1-455.e9, Elsevier, United States (2010).
- Lanigan, R.S. and Yamarik, T.A., "Final Report on the Safety Assessment of Bht(1)," *International Journal of Toxicology* 21(2):19-94, Sage Publications, United States (2002).
- Lapez-Belmonte, J., et al., "Comparative Uterine Effects on Ovariectomized Rats After Repeated Treatment with Different Vaginal Estrogen formulations," *Maturitas* 72(4):353-358, Elsevier/ North Holland Biomedical Press, Ireland (2012).
- Lauer, A.C., et al., "Evaluation of the Hairless Rat as a Model for in Vivo Percutaneous Absorption," *Journal of Pharmaceutical Sciences* 86(1):13-18, Wiley-Liss, United States (1997).
- Leonetti, H.B., et al., "Transdermal Progesterone Cream as an Alternative Progestin in Hormone therapy," *Alternative Therapies in Health and Medicine* 11(6):36-38, InnoVision Communications, United States (2005).
- Madishetti, S.K., et al., "Development of Domperidone Bilayered Matrix Type Transdermal Patches : Physicochemical , in Vitro and Ex Vivo Characterization," *Journal of Faculty of Pharmacy* 18(3):221-229, BioMed Central, England (2010).
- Miles, R.A., et al., "Pharmacokinetics and Endometrial Tissue Levels of Progesterone After Administration by intramuscular and Vaginal Routes : A Comparative Study," *Fertility and Sterility* 62(3):485-490, Elsevier for the American Society for Reproductive Medicine, United States (1994).
- Miller, J.A., et al., "Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast," *Journal of Cancer Therapy* 3(5A), Scientific Research Publishing, United States (2012).
- Nilsson, U., et al., "Analysis of Contact Allergenic Compounds in Oxidized d-Limonene," *Chromatographia* 42:199-205, (1996).
- Non Final Office Action dated Dec. 12, 2011 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Notice of Allowance dated Sep. 11, 2013 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Opinion on Diethylene glycol monoethyl ether, Scientific Committee on Consumer Products, The SCCP adopted this opinion at its 10th plenary,27 pages (2006).
- Otterson, K. "The Drug Quality and Security Act—Mind the Gaps," *The New England Journal of Medicine* 370(2):97-99, Massachusetts Medical Society., United States (2014).
- Palamakula, A., et al., "Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components" *Pharmaceutical Technology* 74-88, (2004).
- Panay, N., et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Parasuraman, S., et al., "Blood Sample Collection in Small Laboratory Animals," *Journal of Pharmacology & Pharmacotherapeutics* 1(2):87-93, Medknow Publications and Media, India (2010).
- Pfaus, J.G., et al., "Selective Facilitation of Sexual Solicitation in the Female Rat by a Melanocortin Receptor Agonist," *Proceedings of the National Academy of Sciences of the United States of America* 101(27):10201-10204, National Academy of Sciences, United States (2004).
- Pickles, V.R. "Cutaneous Reactions to injection of Progesterone Solutions into the Skin," *British Medical Journal* 2(4780):373-374, British Medical Association, England (1952).
- Pinkerton, J.V. "What are the Concerns About Custom-Compounded "Bioidentical" Hormone therapy?," *Menopause* 21(12):1298-1300, Lippincott-Raven Publishers, United States (2014).
- Prausnitz, M.R. and Langer, R., "Transdermal Drug Delivery," *Nature Biotechnology* 26(11):1261-1268, Nature America Publishing, United States (2008).
- Product Safety Assessment, Diethylene Glycol Monoethyl Ether, The Dow Chemical Company Page, 5 Pages (2007).
- Provider Data Sheet, "About Dried Blood Spot Testing," ZRT Laboratory, 3 pages (2014).
- Rahn, D.D., et al., "Vaginal Estrogen for Genitourinary Syndrome of Menopause: A Systematic Review," *Obstetrics and Gynecology* 124(6):1147-1156, Lippincott Williams & Wilkins, United States (2014).
- Reisman, S.A., et al., "Topical Application of the Synthetic Triterpenoid Rta 408 Protects Mice From Radiation-induced Dermatitis," *Radiation Research* 181(5):512-520, Radiation Research Society, United States (2014).
- Ross, D., et al., "Randomized , Double-Blind , Dose-Ranging Study of the Endometrial Effects of a Vaginal Progesterone Gel in Estrogen-Treated Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 177(4):937-941, Elsevier, United States (1997).
- Ruan, X. and Mueck, A.O., "Systemic Progesterone therapy—Oral, Vaginal , injections and Even Transdermal ?," *Maturitas* 79(3):248-255, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Salem, H.F. "Sustained-Release Progesterone Nanosuspension Following intramuscular injection in Ovariectomized Rats," *International Journal of Nanomedicine* 10:943-954,DOVE Medical Press, New Zealand (2010).
- Santen, R.J. "Vaginal Administration of Estradiol : Effects of Dose , Preparation and Timing on Plasma Estradiol Levels," *The Journal of the International Menopause Society* :1-14, Informa Healthcare, England (2014).
- Schutte, S.C. and Taylor, R.N., "A Tissue-Engineered Human Endometrial Stroma That Responds to Cues for Secretory Differentiation , Decidualization , and Menstruation," *Fertility and Sterility* 97(4):997-1003, Elsevier for the American Society for Reproductive Medicine, United States (2012).

US 10,639,375 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Schweikart, K.M., et al., "Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats," *Toxicologic Pathology* 42(8):1188-1196, Sage Publications, United States (2014).
- Shao, R., et al., "Direct Effects of Metformin in the Endometrium : A Hypothetical Mechanism for the Treatment of Women with PCOS and Endometrial Carcinoma," *Journal of Experimental & Clinical Cancer Research* 33:41, BioMed Central, England (2014).
- Shrier, L.A., et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *The Journal of Adolescent Health* 32(3):183-186, Elsevier, United States (2003).
- Siew, A., et al., "Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems" *Pharmaceutical Technology* 28,30-31, (2014).
- Simon, J.A. "What If the Women'S Health Initiative Had Used Transdermal Estradiol and Oral Progesterone instead?," *Menopause* 21(7):769-783, Lippincott-Raven Publishers, United States (2014).
- Smyth, H.F., et al., "A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats," *Food and Cosmetics Toxicology* 2:641-642, Pergamon Press, England (1964).
- Stanczyk, F.Z., et al., "therapeutically Equivalent Pharmacokinetic Profile Across Three Application Sites for Ag200-15 , a Novel Low-Estrogen Dose Contraceptive Patch," *Contraception* 87(6):744-749, Elsevier, United States (2013).
- Sullivan, D.W.Jr., et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology* 72:40-50, Elsevier Science Ltd, England (2014).
- Sun, J. "D-Limonene : Safety and Clinical Applications," *Alternative Medicine Review* 12(3):259-264, Alternative Medicine Review, United States (2007).
- Tang, F.Y., et al., "Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat," *Biology of Reproduction* 31(2):399-413, Society for the Study of Reproduction, United States (1984).
- Tas, M., et al., "Comparison of Antiproliferative Effects of Metformine and Progesterone on Estrogen-induced Endometrial Hyperplasia in Rats," *Gynecological Endocrinology* 29(4):311-314, Informa Healthcare, England (2013).
- Thomas, P. "Characteristics of Membrane Progestin Receptor Alpha (Mpralpha) and Progesterone Membrane Receptor Component 1 (Pgmrc1) and their Roles in Mediating Rapid Progestin Actions," *Frontiers in Neuroendocrinology* 29(2):292-312, Academic Press, United States (2008).
- Tuleu, C., et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying formulation of Progesterone Presented in a Pellet and Liquid form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences* 93(6):1495-1502, Wiley-Liss, United States (2004).
- Ueda, T., et al., "Topical and Transdermal Drug Products," *Pharmaceopeial Forum* 35(3):750-764, (2009).
- Voegtlle, K.M. and Granger, D.A., "Dispatches From the interface of Salivary Bioscience and Neonatal Research," *Frontiers in Endocrinology* 5:25,Frontiers Research Foundation, Switzerland (2014).
- Waddell, B.J. and Bruce, N.W., "The Metabolic Clearance of Progesterone in the Pregnant Rat : Absence of a Physiological Role for the Lung," *Biology of Reproduction* 40(6):1188-1193, Society for the Study of Reproduction, United States (1989).
- Walter, L.M., et al., "the Role of Progesterone in Endometrial Angiogenesis in Pregnant and Ovariectomised Mice," *Reproduction* 129(6):765-777,Reproduction and Fertility by BioScientifica, England (2005).
- Wren, B.G., et al., "Effect of Sequential Transdermal Progesterone Cream on Endometrium , Bleeding Pattern , and Plasma Progesterone and Salivary Progesterone Levels in Postmenopausal Women," *The Journal of the International Menopause Society* 3(3):155-160, Informa Healthcare, England (2000).
- Wu, X., et al., "Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus," *Biology of Reproduction* 69(4):1308-1317, Society for the Study of Reproduction, United States (2003).
- Zava, D. "Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues" Script:4-5.
- Zava, D.T., et al., "Percutaneous absorption of progesterone," *Maturitas* 77:91- 92, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Geelen, M.J.H., et al., "Dietary Medium-Chain Fatty Acids Raise and (n-3) Polyunsaturated Fatty Acids Lower Hepatic Triacylglycerol Synthesis in Rats," *The Journal of Nutrition* 125:2449-2456, American Institute of Nutrition, United States (1995).
- Herman, A and Herman, A.P., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," *Journal of Pharmacy and Pharmacology* 67(4):473-485, Royal Pharmaceutical Society, England (2014).
- Manson, J.E., et al., "Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials," *The Journal of the American Medical Association* 310:1353-1368, American Medical Association, United States (2013).
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 10 pages.
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Notice of Allowance, dated Dec. 15, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Feb. 11, 2015, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Notice of Allowance, dated Feb. 13, 2015, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Notice of Allowance, dated Jan. 22, 2015, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 5 pages.
- Notice of Allowance, dated Jul. 14, 2014, in U.S. Appl. No. 14/099,545, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Jul. 15, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 11 pages.
- Notice of Allowance, dated Nov. 26, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Notice of Allowance, dated Nov. 7, 2014, in U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, 14 pages.
- Office Action, dated Apr. 14, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Office Action, dated Apr. 7, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 10 pages.
- Office Action, dated Dec. 8, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 9 pages.
- Office Action, dated Feb. 18, 2015, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 8 pages.
- Office Action, dated Jul. 18, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jul. 2, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Office Action, dated Jul. 3, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 16 pages.
- Office Action, dated Jul. 30, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jun. 17, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 14 pages.
- Office Action, dated Mar. 12, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 24 pages.
- Office Action, dated Mar. 27, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Office Action, dated Oct. 2, 2014, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Office Action, dated Oct. 1, 2014, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Portman, D., et al., "One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy," *Menopause* 22(11): 7 pages, The North American Menopause Society, United States (2015).

US 10,639,375 B2

Page 14

(56)

References Cited

OTHER PUBLICATIONS

- Rao, R. and Rao, S., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *Journal of Bioequivalence & Bioavailability* 6(4):139-143, Open Access (2014).
- Restriction Requirement, dated Mar. 28, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 7 pages.
- Restriction Requirement, dated Apr. 14, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Apr. 29, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 7 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 9 pages.
- Restriction Requirement, dated Jul. 3, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 6 pages.
- Restriction Requirement, dated Mar. 16, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Mar. 20, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Mar. 26, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 7 pages.
- Restriction Requirement, dated May 13, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Nov. 4, 2014, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 7 pages.
- Schindler, A.E., et al., "Classification and pharmacology of progestins," *Maturitas* 46S1:S7-S16, Elsevier Ireland Ltd., Ireland (2003).
- Sitruk-Ware, R., "Pharmacological profile of progestins," *Maturitas* 47:277-283, Elsevier Ireland Ltd., Ireland (2004).
- Stanczyk, F.Z., "All progestins are not created equal," *Science* 68:879-890, Elsevier Inc., United States (2003).
- Stanczyk, F.Z., et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause* 12(2):232-237, The North American Menopause Society, United States (2005).
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective," *Climacteric* 17(Suppl 2):8-11, International Menopause Society, United Kingdom (2014).
- Stephenson, K., "Transdermal Progesterone: Effects on Menopausal Symptoms and on Thrombotic, Anticoagulant, and Inflammatory Factors in Postmenopausal Women," *International Journal of Pharmaceutical Compounding* 12(4):295-304, IJPC, United States (2008).
- Weintraub, A., "Women Fooled by Untested Hormones From Compounding Pharmacies," *Forbes*, accessed at <http://onforb.es/1LIUmIV>, accessed on Feb. 23, 2015, 3 pages.
- Co-pending U.S. Appl. No. 14/671,655, Inventors Amadio, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- Co-pending U.S. Appl. No. 14/671,651, Inventors Cacase, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- International Search Report and Written Opinion of International Application No. PCT/US2015/023041, Korean Intellectual Property Office, Republic of Korea, dated Jun. 30, 2015, 14 pages.
- Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences* 11(3):42-49, NIPER, India (Jul.-Sep. 2010).
- Abdalla, A., et al., "A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets," *Eur J Pharm Sci* 35(5):457-464, Elsevier, Netherlands (2008).
- Falconer, J.R., et al., "The Effects of Supercritical Carbon Dioxide Processing on Progesterone Dispersion Systems: A Multivariate Study," *AAPS Pharm. Sci. Tech.* 13(4): 1255-1265, Springer, USA (2012).
- Restriction Requirement, dated Feb. 6, 2013, in U.S. Appl. No. 13/684,002, Bernick, B.A., filed Nov. 21, 2012, 9 pages.
- Office Action, dated Oct. 7, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 12 pages.
- Office Action, dated Jul. 15, 2016, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 15 pages.
- Office Action, dated Apr. 21, 2017, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 13 pages.
- Office Action, dated Jul. 2, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 9 pages.
- Notice of Allowance, dated Feb. 10, 2016, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 10 pages.
- Office Action, dated Oct. 26, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 10 pages.
- Office Action, dated Nov. 7, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.
- Office Action, dated Mar. 30, 2016, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 13 pages.
- Office Action, dated Jun. 19, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 11 pages.
- Office Action, dated Mar. 23, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.
- Notice of Allowance, dated Sep. 29, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Notice of Allowance, dated Aug. 4, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 11 pages.
- Notice of Allowance, dated Jun. 15, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Office Action, dated Jul. 20, 2016, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 12 pages.
- Office Action, dated Jun. 16, 2017, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 13 pages.
- Office Action, dated Oct. 8, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 7 pages.
- Notice of Allowance, dated Feb. 1, 2016, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 6 pages.
- Office Action, dated Sep. 28, 2017, in U.S. Appl. No. 15/454,898, Bernick, B.A., filed Mar. 9, 2017, 10 pages.
- Acarturk, Fusun, *Mucoadhesive Vaginal Drug Delivery Systems, Recent Patents on Drug Delivery & Formulation*, vol. 3, pp. 193-205, 2009, Bentham Science Publishers.
- Bhavnani, Bhagu R., et al., Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy, *J Clin Endocrin Metab.*, vol. 97(3), Mar. 2012, The Endocrine Society 2011.
- Bhavnani, Bhagu R., et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ER) and ERA and ERB, *Endocrinology*, Oct. 2008, vol. 149(10), pp. 4857-4870, The Endocrine Society 2008.
- Du, Joanna Y., et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, vol. 20(11), pp. 000-000, The North American Menopause Society 2013.
- Fotherby, K., *Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, Contraception*, vol. 54, pp. 59-69, Elsevier Science, Inc. 1996.
- Fuchs, Katie O., et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Pharmacology/Cosmetology*, vol. 5(1), 2006.
- Hargrove, Joel T., et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, *Estrogen Replacement Therapy, Obstetrics & Gynecology*, vol. 73(4), pp. 606-612, Apr. 1989, The American College of Obstetricians and Gynecologists.
- International Search Report and Written Opinion for International Application No. PCT/US2013/46442, European Patent Office, Netherlands, dated Nov. 1, 2013.
- International Search Report and Written Opinion for International Application No. PCT/US2013/46443, European Patent Office, Netherlands, dated Oct. 31, 2013.
- International Search Report and Written Opinion for International Application No. PCT/US2013/46444, European Patent Office, Netherlands, dated Oct. 31, 2013.

US 10,639,375 B2

Page 15

(56)

References Cited

OTHER PUBLICATIONS

- International Search Report and Written Opinion for International Application No. PCT/US2013/46445, European Patent Office, Netherlands, dated Nov. 1, 2013.
- Kincl. Fred A., et al., Short Communication, Increasing Oral Bioavailability of Progesterone by Formulation, *Journal of Steroid Biochemistry*, vol. 9, pp. 83-84 Pergamon Press 1978, Great Britain.
- The Journal of the North American Menopause Society (NAMS), Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society, *Menopause*, vol. 20(9), pp. 888-902, The North American Menopause Society 2013.
- Patel, Dipen, et al., Transdermal Drug Delivery System: A Review, *The Pharma Innovation, The Pharma Journal*, vol. 1 (4), 2012.
- Sarrel, Philip M., et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, *American Journal of Public Health, Research and Practice*, pp. e1-e6, Published online ahead of print Jul. 18, 2013.
- Shufelt, Chrisandra L., et al., Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, *Menopause: The Journal of the North American Menopause Society (NAMS)*, vol. 21 (3), pp. 000-000, The North American Menopause Society 2013.
- Simon, James, et al., Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet, *Obstetrics & Gynecology*, vol. 112(5), pp. 1053-1060, pp. 373-402, Nov. 2008.
- Sitruk-Ware, Regine, et al., Oral Micronized Progesterone, Contraception, vol. 36(4), Oct. 1987.
- Sitruk-Ware, Regine, Progesterones in hormonal replacement therapy: new molecules, risks, and benefits, *Menopause: The Journal of the North American Menopause Society (NAMS)*, vol. 9(1). pp. 6-15, The North American Menopause Society 2002.
- Smith, Nicholas L., et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, *JAMA Intern Med*, pp. e1-e7, published online Sep. 30, 2013.
- Stanczyk, Frank, et al., Ethynodiol and 17B-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, *Contraception*, vol. 87, pp. 706-727, Elsevier 2013.
- Office Action dated Jul. 16, 2013, in U.S. Appl. No. 13/684,002, Bernick et al., filed Nov. 21, 2012.
- Office Action dated Mar. 20, 2013, in U.S. Appl. No. 13/684,002, Bernick et al., filed Nov. 21, 2012.
- Notice of allowance dated Dec. 6, 2013, in U.S. Appl. No. 13/684,002, Bernick et al., filed Nov. 21, 2012.
- Office Action dated Feb. 18, 2014, in U.S. Appl. No. 14/099,545, Bernick et al., filed Dec. 6, 2013.
- Restriction Requirement dated Feb. 20, 2014, in U.S. Appl. No. 14/099,562, Bernick et al., filed Dec. 6, 2013.
- Restriction Requirement dated Mar. 5, 2014, in U.S. Appl. No. 14/099,623, Bernick et al., filed Dec. 6, 2013.
- Whitehead, M. I., et al., Absorption and Metabolism of Oral Progesterone, *The British Medical Journal*, vol. 280(6217), pp. 825-827, Mar. 22, 1980, BMJ Publishing Group, JSTOR.
- Wood, Charles E., et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, *Breast Cancer Res Treat*, vol. 101, pp. 125-134, published online Jul. 14, 2006, Springer Science+ Business Media B.V. 2006.
- International Search Report and Written Opinion for International Application No. PCT/US2013/023309, European Patent Office, Netherlands, dated Apr. 9, 2013.
- International Search Report for International Application No. PCT/US2012/66406, European Patent Office, Netherlands, dated Jan. 24, 2013.
- Acarturk, "Mucoadhesive Vaginal Drug Delivery System," *Recent Patents on Drug Delivery & Formulation*, 3 (3):193-205, 2009.
- Fuchs et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Aesthetic Dermatology*, 8(1):14-19, 2006.
- Panay et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," DOI: 1177/1754045313489645, min.sagepub.com. *Menopause International: The Integrated Journal of Postreproductive Health* 0(0):1-10, 2013.
- Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," *Drug Development and Industrial Pharmacy*, 35(5):525-547. 2009. Abstract Only.
- Azure Pharma, Inc., "ELESTRIWM—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, 2009.
- Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," *J. Kor. Pharm. Sci.*, 35(3):173-177, 2005.
- Committee of Obstetric Practice, Committee Opinion—No. 522, *Obstetrics & Gynecology*, 119(4):879-882, 2012.
- Diramio. "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia-Masters of Science Thesis, 131 pages, 2004. http://athena.eum.lib.uga.edu/bitstream/handle/10724/7820/diram_i Jackie_a_200412.ms.pdf?sequence=1.
- Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," *International Journal of Pharmaceutics*, 147(2):165-171, 1997. Abstract Only.
- Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," *Critical Reviews in Toxicology*, 30(3):307-345, 2000. Abstract Only.
- Knuth et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," *Advanced Drug Delivery Reviews*, 11(1-2):137-167, 1993. Abstract Only.
- Lucy et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle," *Bioi Reprod.*, 35(2):300-11, 1986. Abstract Only.
- NuGen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, 3 pages, undated.
- NuGest 900™, <http://www.lhehormoneshop.net/nugest900.htm>, 4 pages, undated.
- Panchagnula et al., "Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies," *J Pharm Pharmacol.*, 43(9):609-14, 1991. Abstract Only.
- Sal Ole, "The physicochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5(7):635-648, 1987.
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230. 2004.
- Tahition Noni, "Body Balance Cream," http://products.lni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/, 1 page, undated.
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol.*, 19:106-121,2006. http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf.
- Agog, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, AGOG, No. 141, vol. 123, No. 1, Jan. 2014, *Obstetrics & Gynecology*.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., *Sci Finder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, *SciFinder*, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, *SciFinder*, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.

US 10,639,375 B2

Page 16

(56)

References Cited

OTHER PUBLICATIONS

- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, http://www.biomedcentral.com/content/supplementary/14_75/2859-11-1_06-S2.pdf.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.
- Brandstatter-Kuhnert, M, Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, *Acta*, vo 16, pp. 847-853, 1959, Univ. Innsbruck.
- Brinton, LA, Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. 15 Biol.* (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l'Oestradiol Hemihydrate, *Acta Cryst.*, B28 pp. 560,1972, Bis(dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moleculaire de la Progesterone C21 H3002, *Acta Cryst.*, B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chern.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21 H3002), desoxycorticosterone (C21 H3003), corticosterone (C21 H3004) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chern. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *Sci Finder, Pharmaceutical Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R. R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Ioder, Salima, et al., Physicochemical properties of Progesterone, *Sci Finder*, pp. 1-26, Feb. 24, 2014, American Chern. Society & US Nail. Lib. of Med.
- Johnson, Williams, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotian, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a γ-Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, *Sci Finder*, pp. 1-46, Feb. 24, 2014, American Chern. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, *Sci Finder*, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.

US 10,639,375 B2

Page 17

(56)

References Cited

OTHER PUBLICATIONS

- Stein, Emily A, et al., Progesterone, Sci Finder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chern. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helveticae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Int. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone. USP29, www.pharmacopeia.cn/v29240/usp29nf24sO_m69870.html, search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T, et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. SteroidBiochem. Mol. Biol.* (2013), Elsevier.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning 1: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II. vol. 1 pp. 127-139, 1968, *Mikrochimica Acta*.
- Kuhnert-Brandstaetter, M & Lnder, R, Zur Hydratbildung bei Steroidhormonen, *Sci. Ph arm.*, vol. 41 (2) pp. 109-116, 1973.
- Kuhnert-Brandstatter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr, The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058,2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetii, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1). Jan. 2003.
- Lewis, John G, et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas, The European Menopaus Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vo177, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Bioi.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, 15 vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MON01500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wen Bin, et al., Chemical Properties of Progesterone, Sci Finder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O. et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Moi.Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*,35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progessterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://Ixsr7.oru.edu/~alang/onc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3, 17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Int. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, Sci Finder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in post-menopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisia L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.

US 10,639,375 B2

Page 18

(56)

References Cited

OTHER PUBLICATIONS

- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319,2004, Elsevier.
- Progynova TS 100, available online at file:I:/C:/Users/Caii%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly{D,L-,lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799,1998, Plenum Pub. Corp.
- Sal Ole, Eugene G, Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal CreamTM and HRT CreamTM Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *Sci Finder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A. E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem.Mol. Biol.* (2013), Elsevier.
- Sci Finder Scholar Prednisone Chemical Properties, *Sci Finder*, 2014, pp. 1-7, National Library of Medicine.
- Sci Finder Scholar Prednisone Physical Properties, *Sci Finder*, 2014, pp. 1-10, Natioinal Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chern. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H. C., et al., Physical Properties of Progesterone Selected Refer, *Sci Finder*, pp. 1-5, Feb. 24, 2014, American Chern. Society & US Nail. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaldrich.com/catalog/product/sigma/p7556>.
- Abitec, CapmuIMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmuIMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmuIMCM, Safley Data Sheet, 2011, Janesville, WI.
- Abitec, CapmuIMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmuIPG8, CAS No. 31565-12-5, version 11,2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition ofThevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uklbp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, *Chempro-Edible-Oil-Refining-ISO-TUV-Austria*.
- Corn Refiners Assoc. Com Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M.A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACS IT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/SurfactanUWater, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 147, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Suplement to USP36-NF 31, pp. 6141-6151,2013.
- USP, Lauroyl Polyoxylglycerides, Saftey Data Sheet, US, 5611 Version #02, pp. 1-9,2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot GOL404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chern.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chern, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Office Action, dated Jan. 19, 2018, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 13 pages.
- Office Action, dated Apr. 16, 2018, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 14 pages.

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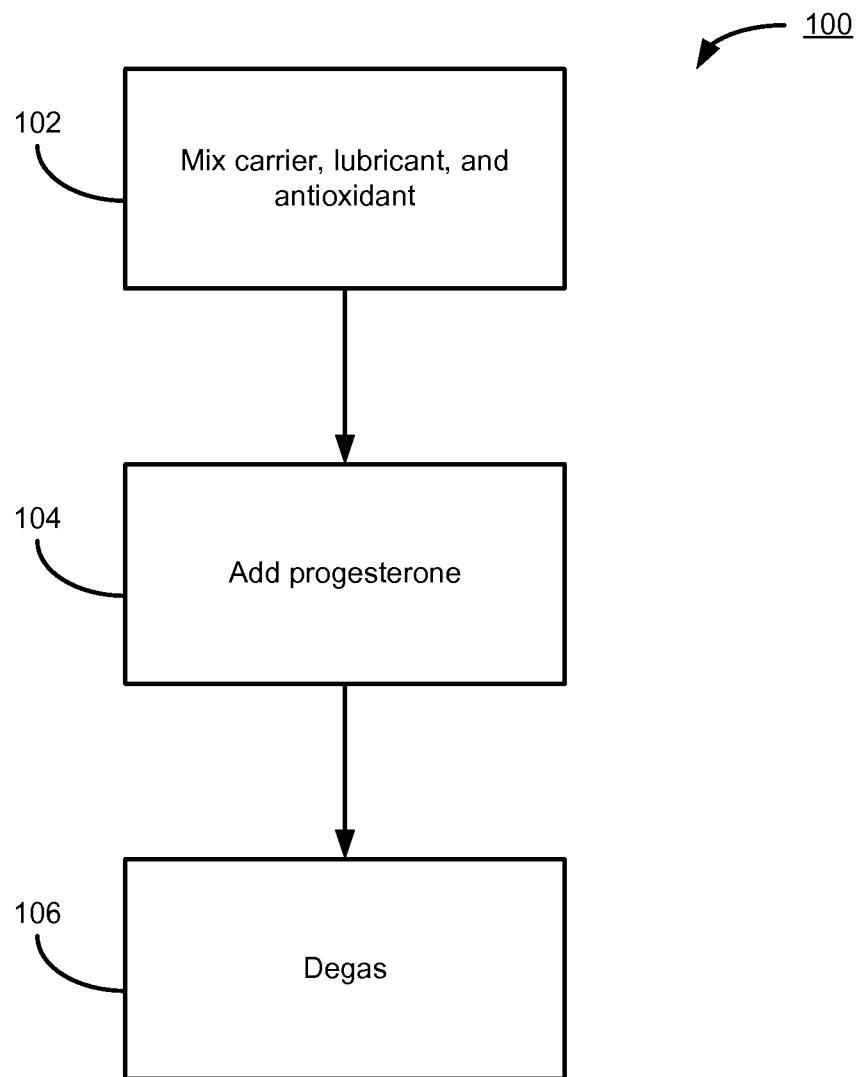


FIG. 1

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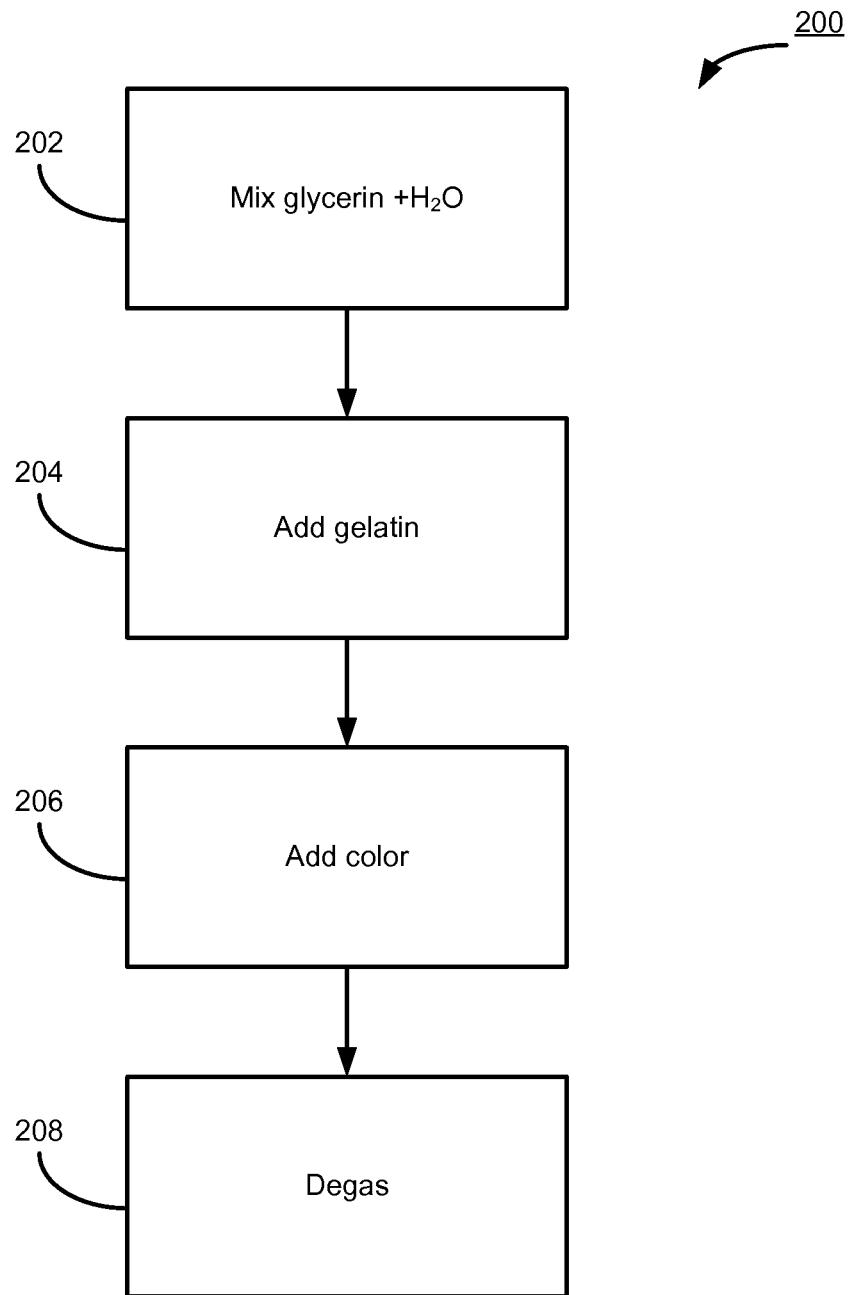


FIG. 2

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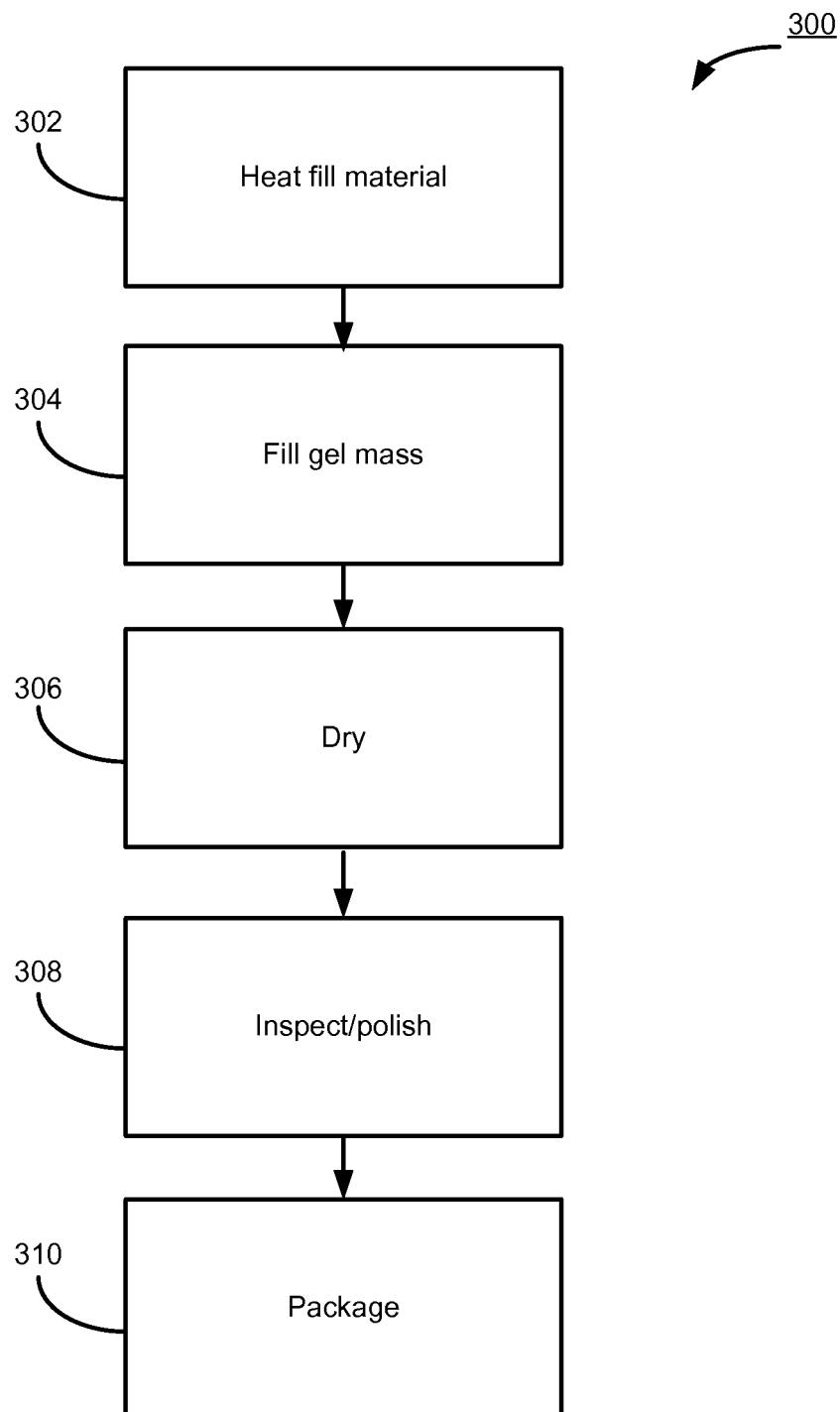


FIG. 3

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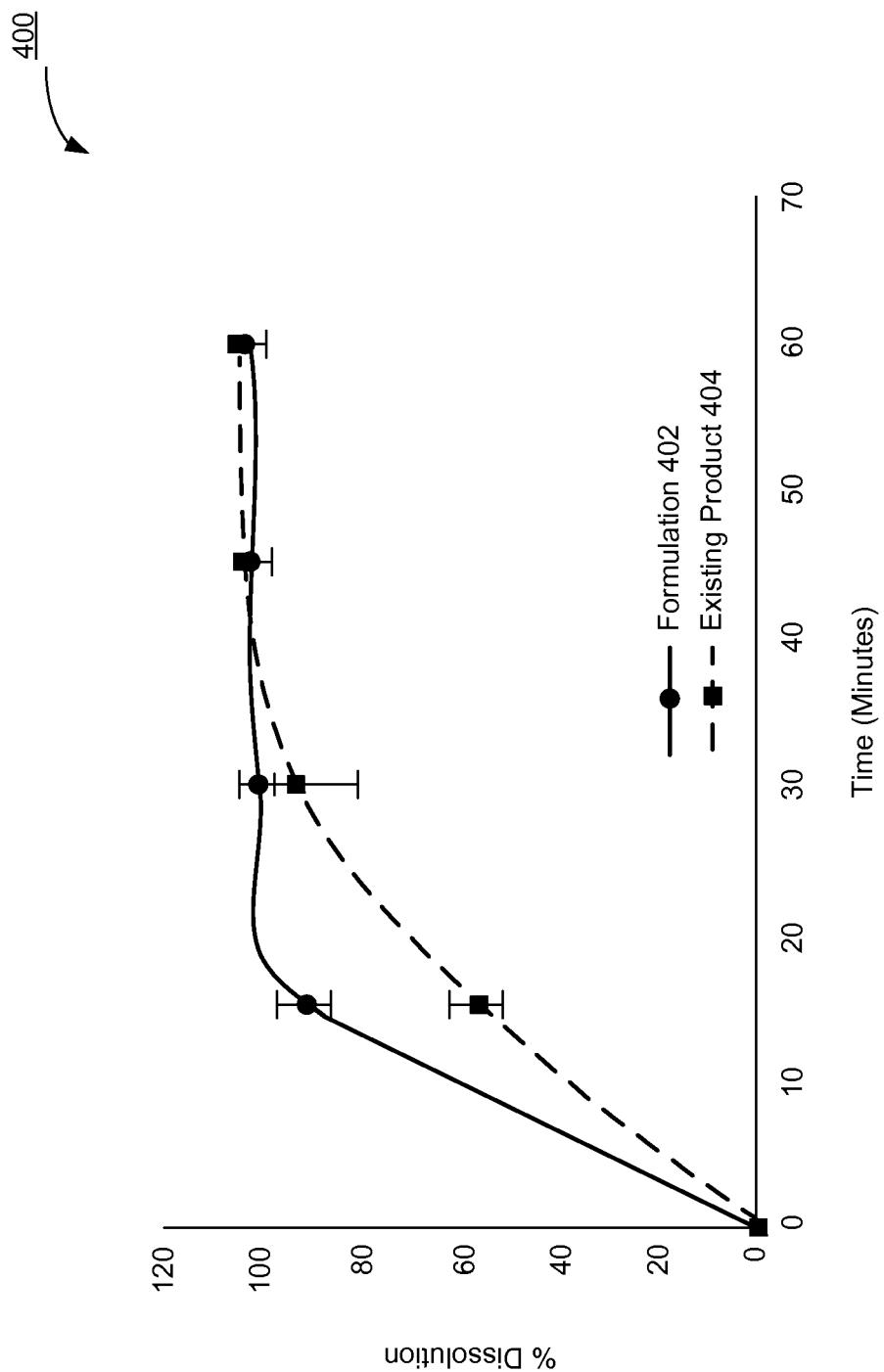


FIG. 4

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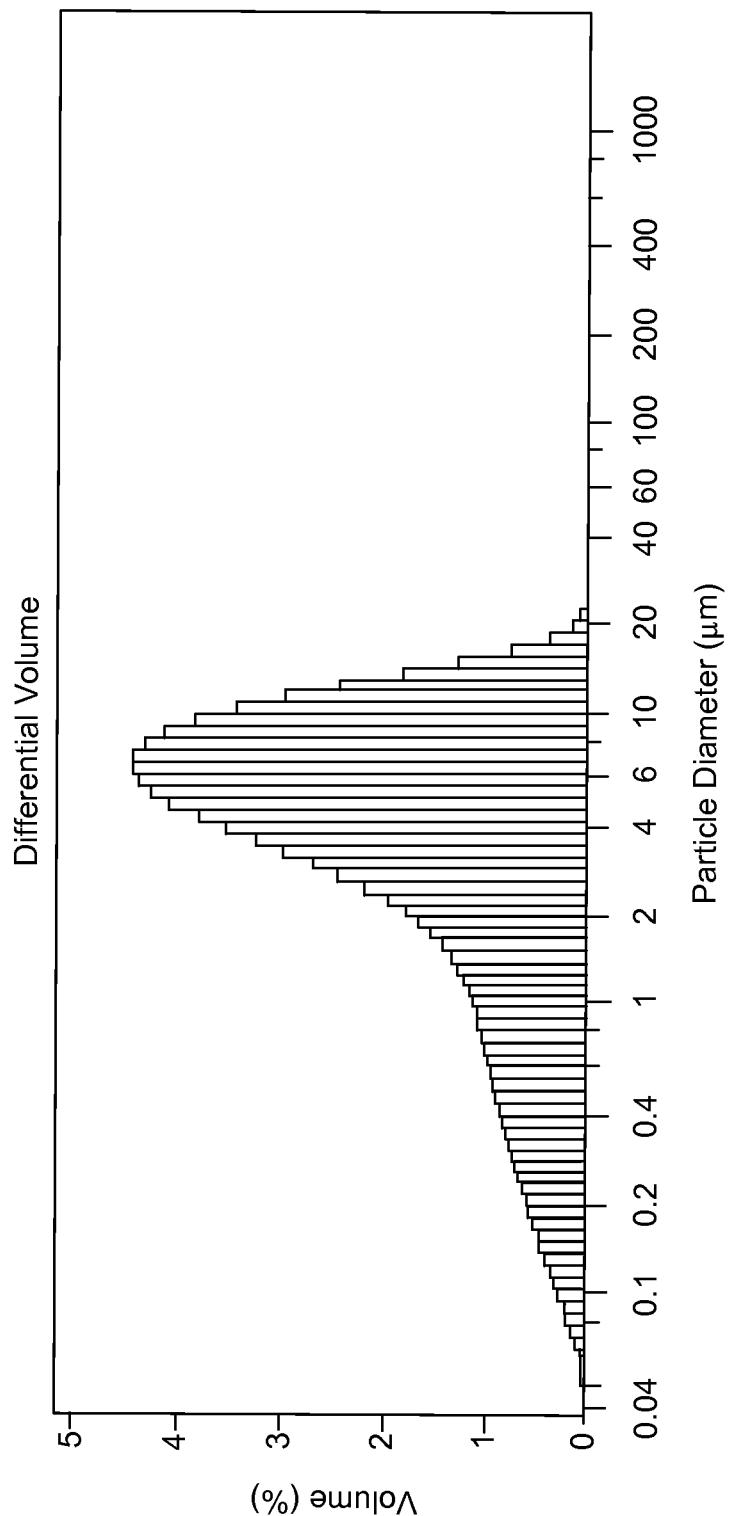


FIG 5.

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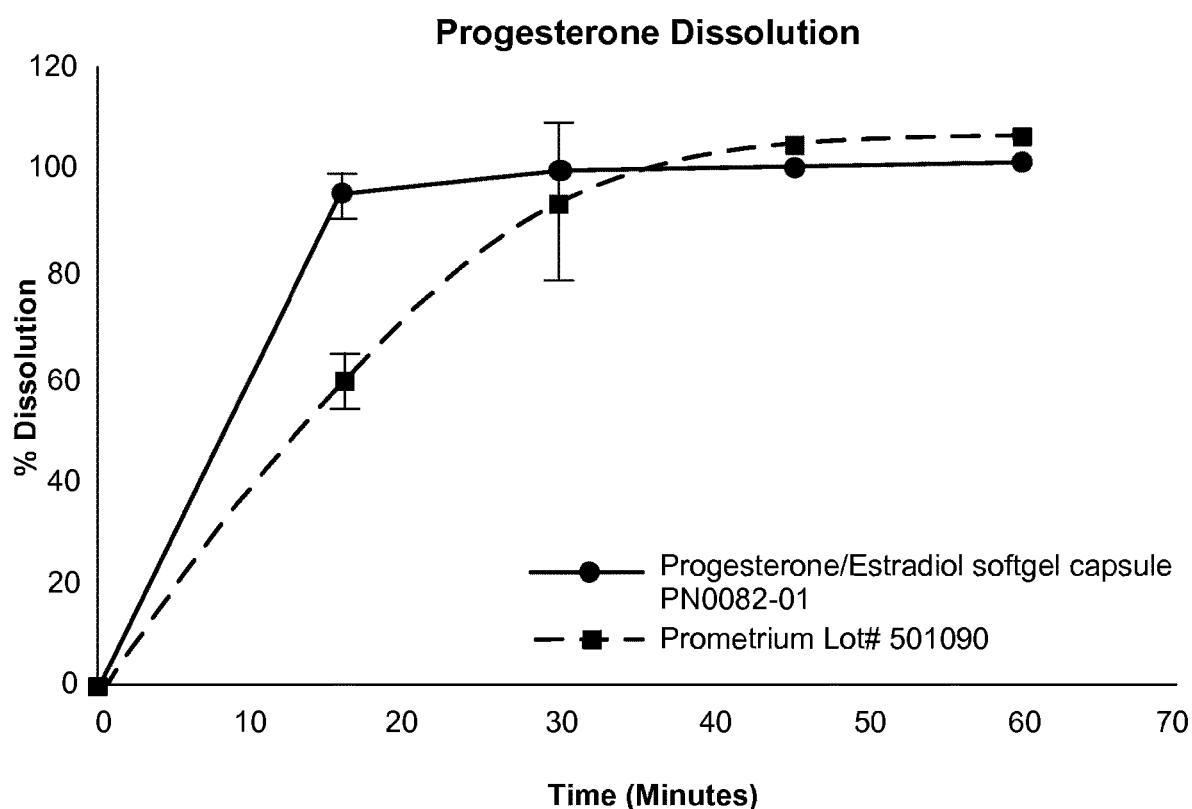


FIG. 6

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1**PROGESTERONE FORMULATIONS****CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a National Stage application under 35 U.S.C. § 371 of International Application Serial No. PCT/US2013/046442, entitled "PROGESTERONE FORMULATIONS" which was filed on 18 Jun. 2013, and claims priority to the following U.S. patent applications: U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012; U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Nov. 21, 2012; U.S. Patent Application Serial No. PCT/US2013/023309, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Jan. 25, 2013; U.S. patent application Ser. No. 13/843,362, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Mar. 15, 2013; and U.S. patent application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF INVENTION

The disclosure relates to progesterone formulations. Various progesterone formulations may be used in hormone therapies for menopausal, peri-menopausal and post-menopausal females, for example, to mitigate side effects from estrogen replacement therapy. In addition, various progesterone formulations may be used to prevent preterm delivery in pregnant women having a shortened cervix.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to supplement hormone levels in women who lack adequate hormone production. It can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones.

HRT is available in various forms. One therapy involves administration of low dosages of one or more estrogen(s) or one or more chemical analogues. Another involves administration of progesterone or one or more chemical analogues. Among other effects, progesterone administration acts to mitigate certain undesirable side effects from estradiol administration or naturally-occurring elevated blood levels including endometrial hyperplasia (thickening) and prevention or inhibition of endometrial cancer. Progesterone is a C-21 steroid sex hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone is hydrophobic, having a reported aqueous solubility of 0.007 ± 0.0 mg/ml. Progesterone is poorly absorbed when administered orally.

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Conventional progesterone therapeutics include the administration of PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug, formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction.

The active ingredient is considered to be structurally identical to naturally occurring progesterone produced by a woman's body (also known as a "bioidentical").

Clinical trials involving PROMETRIUM have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean pharmacokinetic parameters listed in Table 1 (see Table 1, package insert for PROMETRIUM).

TABLE 1

Pharmacokinetic Parameters of PROMETRIUM Capsules			
Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 \pm 21.9	38.1 \pm 37.8	60.6 \pm 72.5
T_{max} (hr)	1.5 \pm 0.8	2.3 \pm 1.4	1.7 \pm 0.6
AUC (0-10)(ng \times hr/ml)	43.3 \pm 30.8	101.2 \pm 66.0	175.7 \pm 170.3

The unusually high variability in the C_{max} and AUC, as evidenced by the large reported standard deviation, indicates that a significant percentage of patients are overdosed or receive a sub-optimal dose.

The presence of peanut oil in the formulation excludes patients who are allergic to peanut oil. Peanut oil, like other peanut products, may act as an allergen. Indeed, there is a portion of the population that has severe reactions to peanut oil. Peanut allergies are becoming a significant health concern. Food allergies are a leading cause of anaphylaxis, with approximately 200 deaths occurring annually in the United States. While incidence and prevalence are not entirely known, it is suspected that about 6% of children and 4% of adults in North America are affected by food allergies. Many food allergies experienced by children are generally outgrown in adulthood with the exception of peanut allergies.

Progesterone and its analogues can be used to treat a variety of medical conditions, including acute diseases or disorders, as well as chronic diseases and disorders associated with long-term declines of natural progesterone levels.

Accordingly, improved formulations of progesterone would be advantageous.

SUMMARY OF THE INVENTION

Various pharmaceutical formulations are disclosed herein. For example, pharmaceutical formulations are disclosed comprising ultra-micronized progesterone. Moreover, pharmaceutical formulations are disclosed comprising formulations of ultra-micronized progesterone, wherein the ultra-micronized progesterone is combined with a suitable excipient.

Thus, in various illustrative embodiments, the invention comprises an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form, in solubilized form, or in micronized and partially soluble form in a carrier that comprises a medium chain fatty

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acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester. In some such embodiments the progesterone is ultra-micronized. In some such embodiments, at least about 80 wt % of the total progesterone is micronized. The fatty acids can be predominantly (>50 wt %): C6 to C12 fatty acids, C6 to C10 fatty acids, C8 to C12 fatty acids, or C8 to C10 fatty acids, the esters can be mono-, di-, or triesters or mixtures thereof, and the glycols can be glycerol, polyethylene glycol or propylene glycol or mixtures thereof. Some embodiments comprise a non-ionic surfactant that comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate embodiments of the disclosure, and together with the description serve to explain the principles of the disclosure.

FIG. 1 illustrates a process to produce fill material in accordance with various embodiments;

FIG. 2 illustrates a process to produce softgel capsules in accordance with various embodiments;

FIG. 3 illustrates a process to produce softgel capsules in accordance with various embodiments; and

FIG. 4 illustrates a dissolution study of a formulation in accordance with various embodiments.

FIG. 5 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 6 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

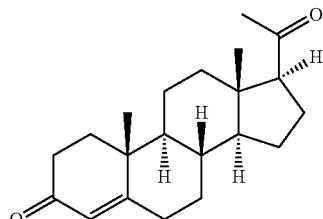
According to various embodiments, a pharmaceutical formulation comprising ultra-micronized progesterone is provided. As described in detail here, various carriers, lubricants, and other excipients may be included. In further embodiments, ultra-micronized progesterone formulations provide improved bioavailability and other pharmacokinetic improvements.

Definitions

Unless otherwise specified, the following definitions apply.

The term “ultra-micronized progesterone,” as used herein, includes micronized progesterone having an X50 value below about 20 microns and/or having an X90 value below about 25 microns.

A chemical structure of progesterone is depicted below:



The term “administer,” “administration,” “deliver” or “delivery” (collectively “administration”), as used herein,

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means administration to the body via, without limitation, tablets, capsules, softgel capsules, injections, transdermal patches, creams, gels, vaginal suppositories including gelcaps or other mechanisms known in the art or hereinafter developed. The term “administration” may also mean direct application of softgel contents into the vagina, such as by accessing the softgel contents opening or rupturing the softgel capsule to liberate the contents therein.

The term “X50,” as used herein, means that half of the particles in a sample are smaller in diameter than a given number. For example, ultra-micronized progesterone having an X50 of 5 microns means that, for a given sample of ultra-micronized progesterone, half of the particles have a diameter of less than 5 microns. In that regard, similar terms, in the form XYY mean that YY percent of the particles in the sample are smaller in diameter than a given number. For example, X90 means that ninety percent of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-contain substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances. For further illustration, C6-C14 fatty acids, C6-C12 fatty acids, and C8-C10 fatty acids are all medium chain fatty acids and may be used in instances in which this specification calls for use of medium chain fatty acids, e.g., medium chain fatty acid esters of glycerol or other glycols.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in gastric juices compared to PROMETRIUM.

The term “gastric juices” means the watery, acidic digestive fluid that is secreted by various glands in the mucous membrane of the stomach and consists chiefly of hydrochloric acid, pepsin, rennin, and mucus.

The term, “API,” as used herein, refers to active pharmaceutical ingredient. In formulations, the API is progesterone.

The term “excipients,” as used herein, refers to non-API substances such as carriers, solvents, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “carrier,” as used herein, means any substance or mixture of substances that may be mixed with or contain an API (e.g., ultra-micronized progesterone).

The term “capsule,” as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products, and includes hard or soft shell capsules.

The term “softgel,” includes soft shell capsules, including soft-gelatin capsules and soft vegetable-based capsules, and soft capsules made from other materials providing the composition of such soft capsules are compatible with the formulations of the various embodiments described herein. A softgel may comprise two primary phases: a gel or vegetable-based capsule and a fill material of the pharmaceutical formulation as described herein.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} and optionally T_{max}.

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The terms "pharmacokinetics" and "pharmacokinetic measurements" include assessments and determinations to study absorption, distribution, metabolism, and excretion of a drug.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone over time.

The term, " C_{max} " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone over time.

The term, " T_{max} " as used herein, refers to the time that it takes for progesterone blood concentration to reach the maximum value.

Optionally, the term, " $T_{1/2}$ " as used herein, refers to the time that it takes for progesterone blood concentration to decline to one-half of the maximum level.

Collectively AUC, C_{max} , and optionally T_{max} and $T_{1/2}$, are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

DESCRIPTION

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone, and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %, based on the weight of the entire fill, i.e., the liquid pharmaceutical formulation.

Other embodiments disclosed herein further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, when compared to equal dosages of PROMETRIUM. Blood level variability is also compared at equal sampling times following administration.

According to the PROMETRIUM prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean PK parameters listed in the following table:

PROMETRIUM Capsules Daily Dose			
Parameter	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T_{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC_{0-10} (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

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In particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure include the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States") in a subject in need of treatment, and with a non-toxic effective amount of said formulations.

As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. Particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The

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Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

In various embodiments, ultra-micronized progesterone has an X50 value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns; and an X90 value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

In various embodiments, ultra-micronized progesterone is formulated with peanut and peanut-oil free excipients.

In various embodiments, the carrier is selected to enhance dissolution and suspension properties of progesterone. In further various embodiments, the carrier is selected to enhance absorption of the API by cells of a mammal. For example, certain carriers may be selected to enhance absorption of the other formulation components, including the API. Absorption may comprise absorption into any cell and particularly absorption into digestive system cells, such as intestinal cells, and cells of the female reproductive system, such as the vagina and the cervix. Selected mono/di/triglycerides are particularly suited to aid in cellular absorption

In various embodiments, the carrier may comprise medium chain fatty acids. Suitable carriers include caproic fatty acid; caprylic fatty acid; capric fatty acid; lauric acid; myristic acid; linoleic acid; succinic acid; glycerin; propylene glycol; caprylic/capric triglycerides; caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; caprylic/capric/succinic triglycerides; polyethylene glycol; propylene glycol dicaprylate/dicaprate; and combinations and derivatives thereof.

Suitable carriers further include esters of saturated coconut and palm kernel oil and derivatives thereof, including fractionated coconut oils and palm kernel oils thereof; and triglycerides of fractionated vegetable fatty acids, and derivatives thereof and combinations thereof. In further various embodiments, the carrier may comprise one or more monoglycerides, diglycerides, triglycerides, and combinations thereof. Such a suitable carrier is available commercially under the trademark MIGLYOL (caprylic/capric triglyceride) (Sasol Germany, GmbH). MIGLYOL products comprise esters of saturated coconut and palm kernel oil-derived caprylic and capric fatty acids, glycerin and/or propylene glycol. Suitable MIGLYOL products include MIGLYOL 810 (Caprylic/Capric Triglyceride) MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 818 (Caprylic/Capric/Linoleic Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride).

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Additional examples include a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the CAPMUL brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof. In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL; TRANSCUTOL, MIGLYOL and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM and a non-ionic surfactant; and CAPMUL MCM and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for suspension and/or solubilization of progesterone. CAPMUL MCM and a non-ionic surfactant, e.g., GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, CAPMUL MCM and GELUCIRE were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be, e.g., 8:1 or greater, e.g., 60 to 70:1.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments, oils used to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, progesterone is soluble in the oils at room temperature, although it may be desirable to warm certain oils initially during manufacture to improve viscosity. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 50° C. In illustrative embodiments, GELUCIRE 44/14 is heated to about 65° C. and CAPMUL MCM is heated to about 40° C. to facilitate mixing of the oil and non-ionic surfactant, although such heating is not necessary to dissolve the estradiol or progesterone.

In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8

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wt % or higher, or 1.0 wt % or higher. Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, CAPMUL MCM, CAPMUL MCM C10 (Glyceryl Monocaprate), CAPMUL MCM C8 (Glyceryl Monocaprylate), and CAPMUL MCM C8 EP (Glyceryl Monocaprylate). These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, MIGLYOL 810 and MIGLYOL 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, CAPMUL PG-8, CAPMUL PG-2L EP/NF (Propylene Glycol Dilaurate), CAPMUL PG-8 NF (Propylene Glycol Monocaprylate), CAPMUL PG-12 EP/NF (Propylene Glycol Monolaurate) and CAPRYOL (Propylene glycol monocaprylate (type II) NF). Other illustrative examples include MIGLYOL 840 (Propylene Glycol Dicaprylate/Dicaprante).

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, GELUCIRE 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of GELUCIRE, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids.

It will be understood that commercially available fatty acid esters of glycerol and other glycols are often prepared from natural oils and therefore may comprise components additional to the fatty acid esters that comprise the predominant (by weight) component(s) and that therefore are used to characterize the product. Such other components may be, e.g., other fatty acid triglycerides, mono- and diesters, free glycerol, or free fatty acids. So, for example, when an oil/solubilizing agent is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for CAPMUL MCM C8 describes CAPMUL MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

By way of further example, MIGLYOL 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

Specifically, a product information sheet for MIGLYOL by SASOL provides the composition of fatty acids as follows:

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-continued

Tests	810	812	818	829	840
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in C8-C10 triglycerides, and a thickening agent, it will be understood that the fatty acid esters component of the formulation may be, e.g., MIGLYOL 812 or a similar product.

By way of further illustration, GELUCIRE 44/14 is generally described as lauroyl polyoxyl-32 glycerides, i.e., polyoxyethylene 32 lauric glycerides (which is a mixture of mono-, di-, and triesters of glycerol and mono- and diesters of PEGs) because the fatty acid composition is 30 to 50% lauric acid and smaller amounts of other fatty acids, e.g., up to 15% caprylic acid, up to 12% capric acid, up to 25% myristic acid, up to 25% palmitic acid, and up to 35% stearic acid. The product may also contain small amounts of non-esterified glycols. Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising C8 to C18 fatty acid esters of glycerol and polyethylene glycol, it will be understood that the thickening agent component of the formulation may be, e.g., GELUCIRE 44/14 or a similar product.

Similarly, where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, it will be understood that the thickening agent component of the formulation may be, e.g., TEFOSE 63 (PEG-6 stearate and ethylene glycol palmitostearate) or a similar product.

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL MCM) and polyethylene glycol glycerides (e.g., GELUCIRE) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The progesterone can be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

In certain embodiments, an anionic and/or a non-ionic surfactant is used. Exemplary non-ionic surfactants may include one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE, including, for example, GELUCIRE 44/11 and GELUCIRE 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, GELUCIRE 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, Tables below. Other non-ionic surfactants include, e.g., LABRASOL (Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF PEG-8

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1

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Caprylic/Capric Glycerides (USA FDA IIG)) (Gattefosse) and LABARAFIL (corn/apricot oil PEG-6 esters) (Gattefosse).

In various embodiments, a lubricant is used. Any suitable lubricant may be used, such as, for example and without limitation, lecithin, and in various embodiments, a mixture of polyethylene glycol ("PEG") esters, glycerides, and PEG, such as is commercially available under the trade name GELUCIRE (Gattefosse, FR) may also be used as a lubricant. Suitable lubricants may also comprise calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, poloxamer, glycols, and phospholipid mixtures. In particular, a mixture of polyethylene glycol esters, glycerides, and PEG such as GELUCIRE 44/14, may be used as a lubricant. GELUCIRE 44/14 is a non-ionic water dispersible surfactant, also known as lauroyl macrogol-32 glycerides EP and lauroyl polyoxyl-32 glycerides NF. In various embodiments, GELUCIRE 44/14 acts as a suspension agent.

In various embodiments, an antioxidant is used. Any suitable antioxidant may be used, such as, for example and without limitation, butylated hydroxytoluene. Butylated hydroxytoluene, a derivative of phenol, is lipophilic and is thus suited to being intermixed with ultra-micronized progesterone and carriers disclosed or contemplated herein.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises progesterone, at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of one or more glycols, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized.

Pharmaceutical formulations in accordance with various embodiments comprise ultra-micronized progesterone. In further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, and a lubricant. In still further embodiments a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, a lubricant, and optionally an antioxidant. In still further

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embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and a medium chain triglyceride as a carrier. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and monoglycerides/diglycerides/triglycerides of caprylic/capric acid as a carrier. Various further embodiments also comprise lecithin and optionally butylated hydroxytoluene.

In additional embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone and at least one carrier, a lubricant, optionally an antioxidant, and other pharmaceutically acceptable excipients. For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Formulations in accordance with various embodiments may be administered alone or combination with one or more other drugs (or as any combination thereof). For example, formulations in accordance with various embodiments may also comprise estradiol.

In various embodiments, ultra-micronized progesterone is administered in a capsule. Capsules may be prepared using one or more film forming polymers. Suitable film forming polymers include natural polymers, such as gelatin, and synthetic film forming polymers, such as modified celluloses. Suitable modified celluloses include, but are not limited to, hydroxypropyl methyl cellulose, methyl cellulose.

Hard or soft shell capsules can be used to administer the API. In certain embodiments, capsules may be prepared by forming the two capsule halves, filling one of the halves with the fill solution, and then sealing the capsule halves together to form the finished capsule.

Hard shell capsules may be prepared by combining the "Body" and the "Cap". The "Body" of the capsule is filled with the "fill mass" and then closed with the "Cap". The "Body"/"Cap" interface is then sealed/banded.

Soft gelatin capsules may be prepared using a rotary die encapsulation process, as further described below.

Suitable shell additives, for either a hard or soft shell capsules, may include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids, and combinations thereof. The main ingredients of the capsule shell is primarily gelatin (or a gelatin substitute for non-gelatin capsules), plasticizer, and purified water. Hard shell and soft shell capsules differ primarily in the amount of plasticizer present that is used in the capsule shell.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include, but are not limited to, glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light-sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

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Colorants can be used for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to minimize cross-linking of the gelatin.

In accordance with various embodiments, a softgel dosage form is used.

A softgel comprises two primary phases: a gel capsule and a fill material. The softgel may comprise a gelatin material in a relatively solid or stiff form. The softgel may define an inner volume that may contain the fill material. Dissolution of the softgel may commence at various points, such as along the digestive tract (mouth, esophagus, stomach and intestines), or other body cavities, such as the vaginal cavity.

As the softgel dissolves, the inner volume may come into fluid communication with the digestive system, allowing the fill material to leach outside the softgel. A softgel may also be punctured, cut, or otherwise opened outside a body. The fill material may then be poured or squeezed outside the gel capsule and applied on or in the body, such as within the vaginal cavity.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl esters (collectively known as "parabens") or combinations thereof.

The fill material may comprise a liquid, such as an oil, a solution, a suspension, or other acceptable forms. The active ingredient or active ingredient may be contained within the liquid.

Formulations in accordance with various embodiments may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Ultra-micronized progesterone in accordance with various embodiments may be formulated as a vaginal suppository or vaginal cream for administration onto the vulva or into the vagina, cervix, or uterus of a human. Capsules (e.g., softgels) containing ultra-micronized progesterone also may be administered vaginally, including insertion of a capsule directly into the vaginal cavity or delivery of such capsule contents into the vaginal cavity. Ultra-micronized progesterone, in accordance with various embodiments, may be formulated for intraperitoneal administration, and atomization, such as with nasal mist administration.

In accordance with various embodiments, enhanced bioavailability of progesterone is provided, such as over conventional progesterone formulations wherein it is well known that commercially available formulations of progesterone are poorly or inconsistently absorbed. While not bound by theory, the elements of the present formulation provide the enhanced performance characteristics as further described herein, including, for example and without limitation, improved bioavailability and the potential to be able to reduce the administered dosage strength compared to

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presently available progesterone formulations. Bioavailability comparisons to commercially available forms, such as tablet forms, may be determined by standard pharmacokinetic techniques

5 In accordance with various embodiments, food effects are reduced, e.g., relative to comparative progesterone products.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

10 Capsules may be arranged in blisters or cartridges or bottles.

According to various embodiments, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having delivery days identified to improve compliance and reduce associated symptoms, among others.

15 One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no API or hormone (e.g., progesterone) may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day

20 may further comprise a single blister or a plurality of blisters. In various embodiments, each dose (e.g., each softgel) may contain ultra-micronized progesterone in amounts of 100 mg, 150 mg, 200 mg, and 250 mg, though other dose ranges are contemplated herein. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

25 Formulations in accordance with various embodiments may be used to treat or prevent preterm delivery in pregnant women, including in certain women having a shortened cervix. In various embodiments, a capsule, for example a softgel capsule, may be opened and the fill material applied in or around the vagina. However, in various embodiments the capsules are taken orally.

30 Formulations in accordance with various embodiments may be used to treat or prevent endometrial hyperplasia.

Formulations in accordance with various embodiments may be used to treat or prevent secondary amenorrhea.

35 Formulations in accordance with various embodiments may be used to mitigate or treat the effects of estradiol supplementation. In particular, formulations in accordance with various embodiments may be co-administered with estradiol and/or co-formulated with estradiol.

40 Formulations in accordance with various embodiments may be used to treat menopause-related symptoms, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy; and osteoporosis and endometrial hyperplasia reduction.

45 Additional objects of the present disclosure include: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

Specific Embodiments

55 Through extensive trial-and-error testing of various fatty acid esters of glycerol and other glycols, embodiments of the

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invention have been invented that have one or more favorable characteristics for development as a human drug product. Such favorable characteristics include those described above, e.g., improved PK and reduced variability.

Such embodiments include an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form suspended in a carrier that comprises a medium chain fatty acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester.

A more specific such embodiment is such formulation wherein the progesterone is ultramicronized.

In certain such embodiments, the progesterone is suspended and/or solubilized in one or more C6 to C12 fatty acid mono-, di-, or triesters of glycerol, e.g., one or more C6 to C14 triglycerides, e.g., one or more C6 to C12 triglycerides, such as one or more C8-C10 triglycerides. An example of a carrier that provides beneficial properties is C8, C10, or C8 and C10 saturated triglycerides, such as but not limited to MIGLYOL, e.g., MIGLYOL 812.

In such general and more specific embodiments, the non-ionic surfactant is a polyethylene glycol saturated or unsaturated fatty acid ester or diester. In certain such embodiments, the non-ionic surfactant comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol. An example of a non-ionic surfactant that provides beneficial properties is GELUCIRE, e.g., GELUCIRE 44/14.

In certain such embodiments, the non-ionic surfactant has a HLB value of about 15. An illustrative example of such surfactant is GELUCIRE 44/14.

As noted above, such formulations are liquid at room temperature, not gels, hard fats, or any other solid form. The non-ionic surfactant serves to increase viscosity. In some such embodiments, the non-ionic surfactant, e.g., GELUCIRE or TEFOSE, may be solid at room temperature and require melting to effect mixing with the estradiol solubilized in fatty acid-glycol esters but the resultant formulation is advantageously liquid, not solid.

The formulation of such embodiments is typically encapsulated in a soft gelatin capsule or other soft capsule.

Typically, such formulations do not comprise a bioadhesive (i.e., muco-adhesive) agent, a gelling agent, or a dispersing agent, or, at least, do not comprise one or two of such components.

In more specific such formulations, the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant are the only essential ingredients. Non-essential ingredients, e.g., colorants, antioxidants or other preservatives, etc., may, of course, be included but other ingredients in amounts that would materially change the solubility of the progesterone, the PK of the encapsulated formulation, or other clinically relevant properties, e.g., other oils or fatty acid esters, lecithin, muco-adherent agents, gelling agents, dispersing agents, or the like would not be included. Such embodiments of the invention may be described as consisting essentially of the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant, as described in the immediately preceding paragraphs describing illustrative embodiments discovered to have favorable characteristics.

An example of such embodiments discovered to have such favorable characteristics is mentioned the product identified in Example 2, Table 3, below.

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EXAMPLES

Example 1

5 In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 2

10	Ingredient	mg/Capsule	%	Function
	Ultra-micronized Progesterone	200.00	30.77	Active
	Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
15	Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
	Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

20 The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 2

30 In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 3

35	Ingredient	%	mg/Capsule	Function
	1. Ultra-micronized Progesterone	30.77	200.00	Active
	2. Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
40	3. Lauroyl polyoxyxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
	4. Butylated Hydroxytoluene	0.03	1.95	Antioxidant
	Total	100	650	

50 In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 3

Progesterone Solubility

55 In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 60 50 mg to 100 mg per capsule. MIGLYOL was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL, including without limitation MIGLYOL 812, may be used in embodiments comprising a suspension of progesterone.

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As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg.

TABLE 4

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM	73.4
CAPMUL PG8	95
MIGLYOL 812	27.8
CAPMUL MCM: GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM: GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM: GELUCIRE 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM in combination with GELUCIRE 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM and GELUCIRE 44/14 system, wherein the ratio of CAPMUL MCM to GELUCIRE 44/14 is 9:1.

TABLE 5

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM:GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM:GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM:GELUCIRE 44/14 (6:4)	57.4

Example 4

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 6

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 7

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 8

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 6

Bioavailability Assessment—Fasted

A randomized single-dose oral bioequivalence study comparing 200 mg ultra-micronized progesterone capsule test product (T) and 200 mg PROMETRIUM® (progesterone) capsules (Abbott Laboratories, Abbott Park, Ill.) reference product (R) is conducted. Subjects are administered a single 200 mg dose of either test product (T) or the reference product (R) under fasting conditions, for example, subjects fasted at least 10.0 hours prior to dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00,

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18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose.

Pharmacokinetic measurements are assessed including C_{max} , AUC and optionally T_{max} . Comparative bioavailability of the test product (T) and reference product are assessed.

Example 7

Bioavailability Assessment—Fed

The procedures for determining bioavailability under fasted conditions are repeated except that subjects are administered a single 200 mg dose of either test product (T) or reference product (R) immediately following a high fat meal, for example, within 30 minutes of dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose. Pharmacokinetic measurements are assessed including C_{max} , AUC and optionally T_{max} . Bioavailability of the test product (T) in reference to the reference product is assessed. The effect of food on the comparative bioavailability of the test product (T) and the reference product (R) are also assessed.

Example 8

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material, i.e. fill mass, preparation 100 is shown. Step 102 comprises mixing a carrier, a lubricant, and an antioxidant as described herein. For example, lecithin and butylated hydroxytoluene may be mixed with one or more medium chain mono-, di- or triglycerides, or combinations thereof. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 104 may comprise mixing ultra-micronized progesterone into the mixture of the carrier, the lubricant, and the antioxidant. A pasty substance is thus formed. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 104 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 106 comprises degassing. The resulting mixture from step 106 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80°±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

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Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/-3° C. Fill material maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Polishing may be performed with isopropyl alcohol.

Example 9

Stability Study

In accordance with various embodiments, formulations in accordance with various embodiments have an exemplary shelf life of 3 months with storage at 25±2° C./60±5% RH in 75 cc HDPE white, opaque bottles with a 38/400 mm white child resistant cap.

Packaging during testing comprises a 75 cc round HDPE bottle and 33 mm cap. A Brasken FPT 300F resin is associated with the cap. Testing criteria include visual appearance, assay of progesterone, dissolution, content uniformity and microbial limits testing.

Three test groups are created. Test group 1 comprises a test at 40° C./75% RH. Test group 2 comprises a test at 30° C./65% RH. Test group 3 comprises a test at 25° C./60% RH. Test group 1 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 1, 2, 3, and 6. Test group 2 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, and 12. Test group 3 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, 12 and 24.

Example 10

A particle size analysis is conducted by using a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the “Beckman Device”). The Beckman Device uses laser

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diffraction to determine particle size. A sample of a formulation in accordance with various embodiments is provided. The Beckman Device particle sensor yields that the sample has an X50 of 6.67 μm , an X75 of 14.78 μm , and an X25 of 2.193 μm .

Example 11

A dissolution study was performed using a formulation in accordance with various embodiments. The results of the dissolution study are shown in FIG. 4.

The dissolution study was performed using a United States Pharmacopoeia dissolution apparatus 3 (reciprocating cylinder) ("USP Apparatus 3"). The USP Apparatus 3 was set to 30 dips per minute. Two hundred fifty mL (250 mL) of a solution of 1N HCl with 3% sodium lauryl sulfate was used at 37° C.

FIG. 4 shows dissolution percentage in the y axis over time in minutes on the x axis. A formulation in accordance with various embodiments is shown having circular dots, and is labeled formulation 402. An existing commercial pharmaceutical product containing progesterone is shown having square dots and is labeled existing product 404. As shown in FIG. 4, formulation 402 reaches a higher level of dissolution in a shorter time than existing product 404.

Example 12

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm , an X75 of 7.442 μm , and an X25 of 1.590 μm . The Beckman Device also yielded that the mean particle size is 4.975 μm , the median particle size is 4.279 μm , the mode particle size is 6.453 μm , and the standard deviation is 3.956 μm . A graph of the particle distribution obtained is shown in FIG. 5.

Example 13

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions. This following study protocol was used to establish bio-availability and bioequivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

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Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
5	Progesterone, USP, micronized	7.14
	Estradiol Hemihydrate, USP Micronized	0.30
	CAPMUL MCM, NF, USP	83.27
	GELUCIRE 44/14, NF	9.29
	Total	100.00
		700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

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In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C.±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 9, below, for progesterone.

TABLE 9

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC _{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
AUC _{0-∞}	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 10, below for progesterone.

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TABLE 10

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC _{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
AUC _{0-∞}	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to PROMETRIUM.

Example 14

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of PROMETRIUM and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from PROMETRIUM. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from PROMETRIUM is attached as FIG. 6.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. The disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad, general meaning of the terms in which the

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appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed:

1. A pharmaceutical composition comprising:
progesterone and an effective amount of estradiol not exceeding 2 mg, wherein the estradiol and progesterone are present in a weight ratio of 1:100;
a medium chain oil; and
a non-ionic surfactant;
further wherein the progesterone is present from about 20 to about 50 weight percent of the composition.
2. The pharmaceutical composition of claim 1, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.
3. The pharmaceutical composition of claim 1, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.
4. The pharmaceutical composition of claim 1, wherein the composition is provided in a gelatin capsule.
5. The pharmaceutical composition of claim 1, wherein the composition provides increased progesterone bioavailability compared to a micronized progesterone suspended in peanut oil.
6. The pharmaceutical composition of claim 1, wherein the medium chain oil comprises at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.
7. The pharmaceutical composition of claim 6, wherein the at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C8 fatty acid mono-, di-, or tri-ester of glycerol.
8. The pharmaceutical composition of claim 6, further comprising a second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol.
9. The pharmaceutical composition of claim 8, wherein the second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C10 fatty acid mono-, di-, or tri-ester of glycerol.
10. The pharmaceutical composition of claim 9, wherein the medium chain oil is CAPMUL MCM.

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11. The pharmaceutical composition of claim 1, comprising 50 mg of progesterone.
12. The pharmaceutical composition of claim 1, comprising 100 mg of progesterone.
13. The pharmaceutical composition of claim 12, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.
14. The pharmaceutical composition of claim 13, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.
15. The pharmaceutical composition of claim 12, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.
16. The pharmaceutical composition of claim 15, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.
17. The pharmaceutical composition of claim 16, wherein the composition is provided in a gelatin capsule.
18. The pharmaceutical composition of claim 16, wherein the composition provides increased progesterone bioavailability compared to a micronized progesterone suspended in peanut oil.
19. The pharmaceutical composition of claim 18, wherein the medium chain oil comprises at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.
20. The pharmaceutical composition of claim 19, wherein the at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C8 fatty acid mono-, di-, or tri-ester of glycerol.
21. The pharmaceutical composition of claim 20, further comprising a second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol.
22. The pharmaceutical composition of claim 21, wherein the second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C10 fatty acid mono-, di-, or tri-ester of glycerol.
23. The pharmaceutical composition of claim 22, wherein the medium chain oil is CAPMUL MCM.

* * * * *

EXHIBIT N



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(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 10,675,288 B2
(45) **Date of Patent:** Jun. 9, 2020

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(58) **Field of Classification Search**

None

See application file for complete search history.

(56)

References Cited

U.S. PATENT DOCUMENTS

1,967,351 A	1/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	6/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopflin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	8/1977	Higuchi et al.
4,071,623 A	1/1978	van der Vies
4,093,709 A	6/1978	Choi et al.
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI1001367-9 A2	7/2012
CA	2044371 A1	12/1991

(Continued)

OTHER PUBLICATIONS

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

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Page 2

(56)	References Cited					
U.S. PATENT DOCUMENTS						
4,215,691 A	8/1980	Wong	5,633,242 A	5/1997	Oettel et al.	
4,237,885 A	12/1980	Wong et al.	5,639,743 A	6/1997	Kaswan et al.	
4,310,510 A	1/1982	Sherman et al.	5,645,856 A	6/1997	Lacy et al.	
4,327,725 A	5/1982	Cortese et al.	5,662,927 A	9/1997	Ehrlich et al.	
4,372,951 A	2/1983	Vorys	5,663,160 A	9/1997	Dumas et al.	
4,384,096 A	5/1983	Sonnabend	5,676,968 A	10/1997	Lipp et al.	
4,393,871 A	7/1983	Vorhauer et al.	5,677,292 A	10/1997	Li et al.	
4,402,695 A	9/1983	Wong	5,686,097 A	11/1997	Crisologo et al.	
4,423,151 A	12/1983	Baranczuk	5,693,335 A	12/1997	Xia et al.	
4,449,980 A	5/1984	Millar et al.	5,694,947 A	12/1997	Lehtinen et al.	
4,610,687 A	9/1986	Fogwell	5,700,480 A	12/1997	Hille et al.	
4,629,449 A	12/1986	Wong	5,709,844 A	1/1998	Arbeit et al.	
4,732,763 A	3/1988	Beck et al.	5,719,197 A	2/1998	Mantelle et al.	
4,738,957 A	4/1988	Laurent et al.	5,735,801 A	4/1998	Caillouette	
4,756,907 A	7/1988	Beck et al.	5,739,176 A	4/1998	Dunn et al.	
4,762,717 A	8/1988	Crowley, Jr.	5,744,463 A	4/1998	Bair	
4,788,062 A	11/1988	Gale et al.	5,747,058 A	5/1998	Tipton et al.	
4,816,257 A	3/1989	Buster et al.	5,762,614 A	6/1998	Garfield et al.	
4,822,616 A	4/1989	Zimmermann et al.	5,770,176 A	6/1998	Nargessi	
4,865,848 A	9/1989	Cheng et al.	5,770,219 A	6/1998	Chiang et al.	
4,900,734 A *	2/1990	Maxson	5,770,220 A	6/1998	Meconi et al.	
		A61K 9/4858	5,770,227 A	6/1998	Dong et al.	
		514/171	5,776,495 A	7/1998	Duclos et al.	
4,906,475 A	3/1990	Kim	5,780,044 A	7/1998	Tipton et al.	
4,942,158 A	7/1990	Sarpotdar et al.	5,780,050 A	7/1998	Jain et al.	
4,961,931 A	10/1990	Wong	5,788,980 A	8/1998	Nabahi	
5,030,629 A	7/1991	Rajadhyaksha	5,788,984 A	8/1998	Schmidt et al.	
5,043,331 A	8/1991	Hirvonen et al.	5,789,442 A	8/1998	Garfield et al.	
5,059,426 A	10/1991	Chiang	5,811,416 A	9/1998	Chwalisz et al.	
5,064,654 A	11/1991	Berner et al.	5,811,547 A	9/1998	Nakamichi et al.	
5,108,995 A	4/1992	Casper	5,814,329 A	9/1998	Shah	
5,128,138 A	7/1992	Blank	5,820,878 A	10/1998	Shimmura et al.	
5,130,137 A	7/1992	Crowley, Jr.	5,827,200 A	10/1998	Caillouette	
5,140,021 A	8/1992	Maxson et al.	5,840,327 A	11/1998	Gale et al.	
5,164,416 A	11/1992	Nagai et al.	5,843,468 A	12/1998	Yum et al.	
5,208,225 A	5/1993	Boissonneault et al.	5,843,979 A	12/1998	Wille et al.	
5,211,952 A	5/1993	Spicer et al.	5,858,394 A	1/1999	Lipp et al.	
5,252,334 A	10/1993	Chiang et al.	5,863,552 A	1/1999	Yue	
5,280,023 A	1/1994	Ehrlich et al.	5,866,603 A	2/1999	Li et al.	
5,288,496 A	2/1994	Lewis	5,869,084 A	2/1999	Paradissis et al.	
5,340,584 A	8/1994	Spicer et al.	5,882,676 A	3/1999	Yum et al.	
5,340,585 A	8/1994	Pike et al.	5,885,612 A	3/1999	Meconi et al.	
5,340,586 A	8/1994	Pike et al.	5,888,533 A	3/1999	Dunn	
5,362,497 A	8/1994	Yamada et al.	5,891,462 A	4/1999	Carrara	
5,382,573 A	1/1995	Casper	5,891,868 A	4/1999	Cummings et al.	
5,393,528 A	2/1995	Staab	5,898,038 A	4/1999	Yallampalli et al.	
5,393,529 A	2/1995	Hoffmann et al.	5,902,603 A	5/1999	Chen et al.	
5,419,910 A	5/1995	Lewis	5,904,931 A	5/1999	Gunther et al.	
5,453,279 A	9/1995	Lee et al.	5,906,830 A	5/1999	Farinas et al.	
5,468,736 A	11/1995	Hodgen	5,912,010 A	6/1999	Wille et al.	
5,474,783 A	12/1995	Miranda et al.	5,916,176 A	6/1999	Caillouette	
5,480,776 A	1/1996	Dullien	RE36,247 E	7/1999	Plunkett et al.	
5,514,673 A	5/1996	Heckenmueller et al.	5,919,477 A	7/1999	Bevan et al.	
5,516,528 A	5/1996	Hughes et al.	5,922,349 A	7/1999	Elliesen et al.	
5,527,534 A	6/1996	Myhling	5,928,666 A	7/1999	Farinas et al.	
5,529,782 A	6/1996	Staab	5,942,243 A	8/1999	Shah	
5,538,736 A	7/1996	Barth et al.	5,942,531 A	8/1999	Diaz et al.	
5,543,150 A	8/1996	Bologna et al.	5,952,000 A	9/1999	Fikstad et al.	
5,547,948 A	8/1996	Barcomb	5,958,446 A	9/1999	Miranda et al.	
5,556,635 A	9/1996	Grognet et al.	5,962,445 A	10/1999	Stewart	
5,565,199 A	10/1996	Page et al.	5,968,919 A	10/1999	Gyurik et al.	
5,567,831 A	10/1996	Li	5,972,372 A	10/1999	Saleh et al.	
5,569,652 A	10/1996	Beier et al.	5,985,311 A	11/1999	Cordes et al.	
5,580,572 A	12/1996	Liorzou et al.	5,985,850 A	11/1999	Falk et al.	
5,582,592 A	12/1996	Kendrick	5,985,861 A	11/1999	Levine et al.	
5,585,370 A	12/1996	Casper	5,993,856 A	11/1999	Ragavan et al.	
5,595,759 A	1/1997	Wright et al.	5,998,568 A	12/1999	de Lacharriere et al.	
5,595,970 A	1/1997	Garfield et al.	6,001,846 A	12/1999	Edwards et al.	
5,605,702 A	2/1997	Math et al.	6,007,835 A	12/1999	Bon Lapillon et al.	
5,607,691 A	3/1997	Solas et al.	6,010,715 A	1/2000	Pollock et al.	
5,607,693 A	3/1997	Bonte et al.	6,013,276 A	1/2000	Teillaud et al.	
5,609,617 A	3/1997	Cady et al.	6,022,562 A	2/2000	Autant et al.	
5,620,705 A	4/1997	Dong et al.	6,024,974 A	2/2000	Li	
5,626,866 A	5/1997	Heiber et al.	6,024,976 A	2/2000	Miranda et al.	
5,629,021 A	5/1997	Wright	6,028,057 A	2/2000	Burns	
5,633,011 A	5/1997	Dong et al.	6,030,948 A	2/2000	Mann et al.	

US 10,675,288 B2

Page 3

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,039,968 A	3/2000	Nabahi	6,455,246 B1	9/2002	Howett et al.	
6,040,340 A	3/2000	Garfield et al.	6,455,517 B1	9/2002	Tanabe et al.	
6,056,972 A	5/2000	Hermsmeyer	6,465,004 B1	10/2002	Houze et al.	
6,060,077 A	5/2000	Meignant	6,465,005 B1	10/2002	Biali et al.	
6,068,853 A	5/2000	Berner et al.	6,465,006 B1	10/2002	Zhang et al.	
6,074,625 A	6/2000	Hawthorne et al.	6,468,526 B2	10/2002	Chrisope	
6,077,531 A	6/2000	Salin-Drouin	6,469,016 B1	10/2002	Place et al.	
6,080,118 A	6/2000	Blythe	6,472,434 B1	10/2002	Place et al.	
6,083,178 A	7/2000	Caillouette	6,479,232 B1	11/2002	Howett et al.	
6,086,916 A	7/2000	Agnus et al.	6,495,160 B2	12/2002	Esposito et al.	
6,087,352 A	7/2000	Trout	6,500,814 B1	12/2002	Hesch	
6,090,404 A	7/2000	Meconi et al.	6,503,896 B1	1/2003	Tanabe et al.	
6,096,338 A	7/2000	Lacy et al.	6,511,969 B1	1/2003	Hermsmeyer	
6,106,848 A	8/2000	Willcox et al.	6,521,250 B2	2/2003	Seibertz et al.	
6,117,446 A	9/2000	Place	6,526,980 B1	3/2003	Tracy et al.	
6,117,450 A	9/2000	Dittgen et al.	6,528,094 B1	3/2003	Savoir et al.	
6,124,362 A	9/2000	Bradbury et al.	6,531,149 B1	3/2003	Meconi et al.	
6,133,251 A	10/2000	Dittgen et al.	6,537,580 B1	3/2003	Savoir et al.	
6,133,320 A	10/2000	Yallampalli et al.	6,538,039 B2	3/2003	Laurent	
6,139,868 A	10/2000	Hoffmann	6,544,196 B2	4/2003	Caillouette	
6,139,873 A	10/2000	Hughes, Jr. et al.	6,544,553 B1	4/2003	Hsia et al.	
6,149,935 A	11/2000	Tenzel et al.	6,548,053 B1	4/2003	Murray et al.	
6,153,216 A	11/2000	Cordes et al.	6,548,491 B2	4/2003	Tanabe et al.	
6,165,491 A	12/2000	Grasset et al.	6,551,611 B2	4/2003	Elliesen et al.	
6,165,975 A	12/2000	Adams et al.	6,555,131 B1	4/2003	Wolff et al.	
6,187,323 B1	2/2001	Aiache et al.	6,562,367 B1	5/2003	Wolff et al.	
6,187,339 B1	2/2001	de Haan et al.	6,562,370 B2	5/2003	Luo et al.	
6,190,331 B1	2/2001	Caillouette	6,562,790 B2	5/2003	Chein	
6,201,072 B1	3/2001	Rathi et al.	6,569,463 B2	5/2003	Patel et al.	
6,217,886 B1	4/2001	Rubinstein et al.	6,583,129 B1	6/2003	Mazer et al.	
6,225,297 B1	5/2001	Stockemann et al.	6,586,006 B2	7/2003	Roser et al.	
6,227,202 B1	5/2001	Matapurkar	6,589,549 B2	7/2003	Shih et al.	
6,228,383 B1	5/2001	Hansen et al.	6,593,317 B1	7/2003	de Ziegler et al.	
6,228,852 B1	5/2001	Shaak	6,599,519 B1	7/2003	Seo et al.	
6,242,509 B1	6/2001	Macqueen et al.	6,610,325 B1	8/2003	Meignant	
6,245,811 B1	6/2001	Horrobin et al.	6,610,652 B2	8/2003	Adams et al.	
6,262,115 B1	7/2001	Guitard et al.	6,610,670 B2	8/2003	Bickensfeld et al.	
6,267,984 B1	7/2001	Hamlin et al.	6,610,674 B1	8/2003	Schreiber	
6,274,165 B1	8/2001	Meconi et al.	6,635,274 B1	10/2003	Carter et al.	
6,277,418 B1	8/2001	Marakverich et al.	6,638,528 B1	10/2003	Kanios	
6,283,927 B1	9/2001	Caillouette	6,638,536 B2	10/2003	Savoir et al.	
6,284,263 B1	9/2001	Place	6,645,528 B1	11/2003	Straub et al.	
6,287,588 B1	9/2001	Shih et al.	6,649,155 B1	11/2003	Dunlop et al.	
6,287,693 B1	9/2001	Savoir et al.	6,653,298 B2	11/2003	Potter et al.	
6,294,188 B1	9/2001	Ragavan et al.	6,656,929 B1	12/2003	Agnus et al.	
6,294,192 B1	9/2001	Patel et al.	6,660,726 B2	12/2003	Hill et al.	
6,294,550 B1	9/2001	Place et al.	6,663,608 B2	12/2003	Rathbone et al.	
6,299,900 B1	10/2001	Reed et al.	6,663,895 B2	12/2003	Savoir et al.	
6,303,132 B1	10/2001	Nelson	6,664,296 B1	12/2003	Meignant	
6,303,588 B1	10/2001	Danielov	6,682,757 B1	1/2004	Wright	
6,306,841 B1	10/2001	Place et al.	6,692,763 B1	2/2004	Cummings et al.	
6,306,914 B1	10/2001	de Ziegler et al.	6,708,822 B1	3/2004	Muni	
6,309,669 B1	10/2001	Setterstrom et al.	6,716,454 B2	4/2004	Meignant	
6,309,848 B1	10/2001	Howett et al.	6,743,815 B2	6/2004	Huebner et al.	
6,312,703 B1	11/2001	Orthofer et al.	6,747,018 B2	6/2004	Tanabe et al.	
6,328,987 B1	12/2001	Marini	6,750,291 B2	6/2004	Kim et al.	
6,342,491 B1	1/2002	Dey et al.	6,756,208 B2	6/2004	Griffin et al.	
6,344,211 B1	2/2002	Hille	6,776,164 B2	8/2004	Bunt et al.	
6,372,209 B1	4/2002	Chrisope	6,787,152 B2	9/2004	Kirby et al.	
6,372,245 B1	4/2002	Vo et al.	6,787,531 B1	9/2004	Hilman et al.	
6,372,246 B1	4/2002	Wei et al.	6,805,877 B2	10/2004	Massara et al.	
6,387,390 B1	5/2002	Deaver et al.	6,809,085 B1	10/2004	Elson et al.	
6,402,705 B1	6/2002	Caillouette	6,818,226 B2	11/2004	Reed et al.	
6,416,778 B1	7/2002	Ragavan et al.	6,821,524 B2	11/2004	Marini	
6,420,352 B1	7/2002	Knowles	6,841,716 B1	1/2005	Tsutsumi	
6,423,039 B1	7/2002	Rathbone et al.	6,844,334 B2	1/2005	Hill et al.	
6,423,683 B1	7/2002	Heaton et al.	6,855,703 B1	2/2005	Hill et al.	
6,432,438 B1	8/2002	Shukla	6,860,859 B2	3/2005	Mehrotra et al.	
6,436,633 B1	8/2002	Kreider et al.	6,866,865 B2	3/2005	Hsia et al.	
6,440,454 B1	8/2002	Santoro et al.	6,869,969 B2	3/2005	Heubner et al.	
6,444,224 B1	9/2002	Rathbone et al.	6,878,518 B2	4/2005	Whitehead	
6,444,234 B1	9/2002	Kirby et al.	6,901,278 B1	5/2005	Notelovitz	
6,451,300 B1	9/2002	Leyba et al.	6,905,705 B2	6/2005	Palm et al.	
6,451,339 B2	9/2002	Patel et al.	6,911,211 B2	6/2005	Tamarkin et al.	
6,451,779 B1	9/2002	Hesch	6,911,438 B2	6/2005	Wright	

US 10,675,288 B2

Page 4

(56)	References Cited				
U.S. PATENT DOCUMENTS					
6,923,988 B2	8/2005	Patel et al.	7,687,485 B2	3/2010	Levinson et al.
6,924,274 B2	8/2005	Lardy et al.	7,694,683 B2	4/2010	Callister et al.
6,932,983 B1	8/2005	Straub et al.	7,704,983 B1	4/2010	Hodgen et al.
6,939,558 B2	9/2005	Massara et al.	7,727,720 B2	6/2010	Dhallan
6,943,021 B2	9/2005	Klausner et al.	7,732,408 B2	6/2010	Josephson et al.
6,958,327 B1	10/2005	Hillisch et al.	7,749,989 B2	7/2010	Hill et al.
6,960,337 B2	11/2005	Pike et al.	7,767,656 B2	8/2010	Shoichet et al.
6,962,691 B1	11/2005	Lulla et al.	7,799,769 B2	9/2010	White et al.
6,962,908 B2	11/2005	Aloba et al.	7,815,936 B2	10/2010	Hasenzahl et al.
6,967,194 B1	11/2005	Matsuo et al.	7,815,949 B2	10/2010	Cohen
6,974,569 B2	12/2005	Boyd et al.	7,829,115 B2	11/2010	Besins et al.
6,977,250 B2	12/2005	Rodriguez	7,829,116 B2	11/2010	Frye et al.
6,978,945 B2	12/2005	Wong et al.	RE42,012 E	12/2010	Deaver et al.
6,987,129 B2	1/2006	Mak et al.	7,850,992 B2	12/2010	Hwang et al.
6,995,149 B1	2/2006	Reilhac et al.	7,854,753 B2	12/2010	Kraft et al.
7,004,321 B1	2/2006	Hackbarth et al.	7,858,607 B2	12/2010	Mamchur
7,005,429 B2	2/2006	Dey et al.	RE42,072 E	1/2011	Deaver et al.
7,011,846 B2	3/2006	Shojaei et al.	7,862,552 B2	1/2011	McIntyre et al.
7,018,992 B2	3/2006	Koch et al.	7,867,990 B2	1/2011	Schultz et al.
7,030,104 B2	4/2006	Paris et al.	7,871,643 B2	1/2011	Lizio et al.
7,030,157 B2	4/2006	Ke et al.	7,879,830 B2	2/2011	Wiley
RE39,104 E	5/2006	Duclos et al.	7,884,093 B2	2/2011	Creasy et al.
7,074,779 B2	7/2006	Sui et al.	7,925,519 B2	4/2011	Greene
7,083,590 B1	8/2006	Bunt et al.	7,939,104 B2	5/2011	Barbera et al.
7,091,213 B2	8/2006	Metcalf, III et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,094,228 B2	8/2006	Zhang et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
7,097,853 B1	8/2006	Keister et al.	7,945,459 B2	5/2011	Grace et al.
7,101,342 B1	9/2006	Caillouette	7,960,368 B2	6/2011	Rao et al.
7,105,573 B2	9/2006	Krajcik et al.	7,989,436 B2	8/2011	Hill et al.
7,135,190 B2	11/2006	Piao et al.	7,989,487 B2	8/2011	Welsh et al.
7,153,522 B1	12/2006	Ikeura et al.	8,022,053 B2	9/2011	Mueller et al.
7,163,681 B2	1/2007	Giles-Komar et al.	8,048,017 B2	11/2011	Xu
7,163,699 B2	1/2007	Besse	8,048,869 B2	11/2011	Bunschoten et al.
7,175,850 B2	2/2007	Cevc	8,063,030 B2	11/2011	Ellman
7,179,799 B2	2/2007	Hill et al.	8,071,576 B2	12/2011	Visser et al.
7,196,074 B2	3/2007	Blye et al.	8,071,729 B2	12/2011	Giles-Komar et al.
7,198,800 B1	4/2007	Ko	8,075,916 B2	12/2011	Park et al.
7,198,801 B2	4/2007	Carrara et al.	8,075,917 B2	12/2011	Park et al.
7,226,910 B2	6/2007	Wilson et al.	8,076,317 B2	12/2011	Kulmann
7,247,625 B2	7/2007	Zhang et al.	8,076,319 B2	12/2011	Leonard
7,250,446 B2	7/2007	Sangita et al.	8,080,553 B2	12/2011	Auspitz et al.
7,267,829 B2	9/2007	Kirby et al.	8,088,605 B2	1/2012	Beudet et al.
7,300,926 B2	11/2007	Prokai et al.	8,096,940 B2	1/2012	Iverson et al.
7,303,763 B2	12/2007	Ho	8,101,209 B2	1/2012	Legrand et al.
7,317,037 B2	1/2008	Fensome et al.	8,101,773 B2	1/2012	Smith et al.
7,329,654 B2	2/2008	Kanojia et al.	8,114,152 B2	2/2012	Furst
7,335,650 B2	2/2008	Potter et al.	8,114,434 B2	2/2012	Sasaki et al.
7,374,779 B2	5/2008	Chen et al.	8,114,442 B2	2/2012	Tucker et al.
7,378,404 B2	5/2008	Peters et al.	8,119,741 B2	2/2012	Pavlín
7,381,427 B2	6/2008	Ancira et al.	8,121,886 B2	2/2012	Azar
7,387,789 B2	6/2008	Klose et al.	8,124,118 B2	2/2012	Lennernaes et al.
7,388,006 B2	6/2008	Schmees et al.	8,124,595 B2	2/2012	Boissonneault
7,414,043 B2	8/2008	Kosemund et al.	8,147,561 B2	4/2012	Binmoeller
7,427,413 B2	9/2008	Savoir et al.	8,148,546 B2	4/2012	Baasner et al.
7,427,609 B2	9/2008	Leonard	8,158,613 B2	4/2012	Staniforth et al.
7,429,576 B2	9/2008	Labrie	8,158,614 B2	4/2012	Lambert et al.
7,431,941 B2	10/2008	Besins et al.	8,163,722 B2	4/2012	Savoir et al.
7,456,159 B2	11/2008	Houze et al.	8,177,449 B2	5/2012	Watkinson et al.
7,459,445 B2	12/2008	Hill et al.	8,182,833 B2	5/2012	Hermsmeyer
7,465,587 B2	12/2008	Imrich	8,187,615 B2	5/2012	Friedman
7,470,433 B2	12/2008	Carrara et al.	8,187,640 B2	5/2012	Dunn
7,485,666 B2	2/2009	Villaneuva et al.	8,195,403 B2	6/2012	Wood, Jr. et al.
7,497,855 B2	3/2009	Ausiello et al.	8,202,736 B2	6/2012	Mousa et al.
7,498,303 B2	3/2009	Arnold et al.	8,217,024 B2	7/2012	Ahmed et al.
7,534,765 B2	5/2009	Gregg et al.	8,221,785 B2	7/2012	Chien
7,534,780 B2	5/2009	Ring et al.	8,222,008 B2	7/2012	Thoene
7,550,142 B2	6/2009	Giles-Komar et al.	8,222,237 B2	7/2012	Narkunan et al.
7,563,565 B1	7/2009	Matsuo et al.	8,227,454 B2	7/2012	Hill et al.
7,569,274 B2	8/2009	Alphonse et al.	8,227,509 B2	7/2012	Castro et al.
7,572,779 B2	8/2009	Aloba et al.	8,241,664 B2	8/2012	Dudley et al.
7,572,780 B2	8/2009	Hermsmeyer	8,247,393 B2	8/2012	Ahmed et al.
7,589,082 B2	9/2009	Savoir et al.	8,257,724 B2	9/2012	Cromack et al.
7,671,027 B2	3/2010	Loumaye	8,257,725 B2	9/2012	Cromack et al.
7,674,783 B2	3/2010	Hermsmeyer	8,268,352 B2	9/2012	Karan et al.
7,687,281 B2	3/2010	Roth et al.	8,268,806 B2	9/2012	Labrie
			8,268,878 B2	9/2012	Johnson et al.
			8,273,730 B2	9/2012	Fernandez et al.
			8,287,888 B2	10/2012	Song et al.
			8,288,366 B2	10/2012	Gonzalez et al.

US 10,675,288 B2

Page 5

(56)	References Cited						
U.S. PATENT DOCUMENTS							
8,318,898 B2	11/2012 Fasel et al.		8,933,059 B2 *	1/2015 Bernick	A61K 31/57		
8,324,193 B2	12/2012 Lee et al.				424/452		
8,329,680 B2	12/2012 Evans et al.		8,987,237 B2 *	3/2015 Bernick	A61K 9/16		
8,337,814 B2	12/2012 Osbakken et al.				424/452		
8,344,007 B2	1/2013 Chui et al.		8,987,238 B2 *	3/2015 Bernick	A61K 31/57		
8,349,820 B2	1/2013 Zeun et al.				424/452		
8,353,863 B2	1/2013 Imran		8,993,548 B2 *	3/2015 Bernick	A61K 9/16		
8,357,723 B2	1/2013 Satyam				424/452		
8,361,995 B2	1/2013 Schramm		8,993,549 B2 *	3/2015 Bernick	A61K 9/16		
8,362,091 B2	1/2013 Besonov et al.				424/452		
8,372,424 B2	2/2013 Berry et al.		9,012,434 B2 *	4/2015 Bernick	A61K 31/57		
8,372,806 B2	2/2013 Bragagna et al.				424/452		
8,377,482 B2	2/2013 Laurie et al.		9,114,145 B2 *	8/2015 Bernick	A61K 9/16		
8,377,994 B2	2/2013 Drechsler et al.		9,114,146 B2 *	8/2015 Bernick	A61K 9/16		
8,394,759 B2	3/2013 Barathur et al.		9,180,091 B2	11/2015 Bernick et al.			
8,415,332 B2	4/2013 Reape et al.		9,248,136 B2 *	2/2016 Bernick	A61K 9/16		
8,420,111 B2	4/2013 Herrmsmeyer		9,289,382 B2	3/2016 Bernick et al.			
8,435,561 B2	5/2013 Besins et al.		9,301,920 B2 *	4/2016 Bernick	A61K 31/57		
8,435,972 B2	5/2013 Sayeed et al.		9,931,349 B2	4/2018 Shadiack et al.			
8,449,879 B2	5/2013 Laurent et al.		10,052,386 B2	8/2018 Bernick et al.			
8,450,108 B2	5/2013 Boyce		10,258,630 B2	4/2019 Mirkin et al.			
8,454,945 B2	6/2013 Narain et al.		2001/0005728 A1	2/2001 Guittard et al.			
8,455,468 B2	6/2013 Kellermann et al.		2001/0009673 A1	7/2001 Gunther et al.			
8,461,138 B2	6/2013 Boissonneau		2001/0021816 A1	9/2001 Caillouette			
8,476,252 B2	7/2013 Pickersgill et al.		2001/0023261 A1	9/2001 Ryoo et al.			
8,481,488 B2	7/2013 Carter		2001/0027189 A1	10/2001 Bennink et al.			
8,486,374 B2	7/2013 Zlatkis et al.		2001/0029357 A1	10/2001 Bunt et al.			
8,486,442 B2	7/2013 Yamaji et al.		2001/0031747 A1	10/2001 de Ziegler et al.			
8,492,368 B2	7/2013 Lewandowski et al.		2001/0032125 A1	10/2001 Bhan et al.			
8,507,467 B2	8/2013 Ueda et al.		2001/0034340 A1	10/2001 Pickar			
8,512,693 B2	8/2013 Azevedo et al.		2012/0269878 A2	10/2001 Cantor et al.			
8,512,754 B2	8/2013 Needham		2001/0053383 A1	12/2001 Sablotsky et al.			
8,518,376 B2	8/2013 Schuz et al.		2001/0056068 A1	12/2001 Chwalisz et al.			
8,536,159 B2	9/2013 Zeng et al.		2002/0012710 A1	1/2002 Lansky			
8,540,967 B2	9/2013 Trivedi et al.		2002/0026158 A1	2/2002 Rathbone et al.			
8,541,400 B2	9/2013 Joabsson et al.		2002/0028788 A1	3/2002 Bunt et al.			
8,551,462 B2	10/2013 Marenus et al.		2002/0035070 A1	3/2002 Gardlik et al.			
8,551,508 B2	10/2013 Lee et al.		2002/0058648 A1	5/2002 Hammerly			
8,557,281 B2	10/2013 Tuominen et al.		2002/0058926 A1	5/2002 Rathbone et al.			
8,568,374 B2	10/2013 de Graaff et al.		2002/0064541 A1	5/2002 Lapidot et al.			
8,591,951 B2	11/2013 Kohn et al.		2002/0076441 A1	6/2002 Shih et al.			
8,613,951 B2	12/2013 Troiano et al.		2002/0102308 A1	8/2002 Wei et al.			
8,633,178 B2 *	1/2014 Bernick	A61K 9/16	2002/0107230 A1	8/2002 Waldon et al.			
		424/452	2002/0114803 A1	8/2002 Deaver et al.			
			2002/0119174 A1	8/2002 Gardlik et al.			
			2002/0119198 A1	8/2002 Gao et al.			
8,633,180 B2	1/2014 Zeng et al.		2002/0132801 A1	9/2002 Heil et al.			
8,636,787 B2	1/2014 Sabaria		2002/0137749 A1	9/2002 Levinson et al.			
8,636,982 B2	1/2014 Schuz et al.		2002/0142017 A1	10/2002 Simonnet			
8,653,129 B2	2/2014 Fein et al.		2002/0151530 A1	10/2002 Leonard et al.			
8,658,627 B2	2/2014 Voskuhl		2002/0156394 A1	10/2002 Mehrotra et al.			
8,658,628 B2	2/2014 Baucom		2002/0169150 A1	11/2002 Pickar			
8,663,681 B2	3/2014 Ahmed et al.		2002/0169205 A1	11/2002 Garfield et al.			
8,663,692 B2	3/2014 Mueller et al.		2002/0173510 A1	11/2002 Levinson et al.			
8,663,703 B2	3/2014 Moldavski et al.		2002/0193356 A1	12/2002 Van Beek et al.			
8,664,207 B2	3/2014 Zheng et al.		2002/0193758 A1	12/2002 Sandberg			
8,669,293 B2	3/2014 Sharoni et al.		2002/0197286 A1	12/2002 Brandman et al.			
8,679,552 B2	3/2014 Guthery		2003/0003139 A1	1/2003 Gunther et al.			
8,694,358 B2	4/2014 Tryfon		2003/0004145 A1	1/2003 Leonard			
8,697,127 B2	4/2014 Sah		2003/0007994 A1	1/2003 Bunt et al.			
8,697,710 B2	4/2014 Zeng et al.		2003/0027772 A1	2/2003 Breton			
8,703,105 B2	4/2014 Besonov et al.		2003/0091620 A1	2/2003 Venkateshwaran et al.			
8,709,385 B2	4/2014 Schuz et al.		2003/0044453 A1	3/2003 Volkel et al.			
8,709,451 B2	4/2014 Rapoport et al.		2003/0049307 A1	3/2003 Gyurik			
8,715,735 B2	5/2014 Funke et al.		2003/0064097 A1	4/2003 Patel et al.			
8,721,331 B2	5/2014 Raghuprasad		2003/0064975 A1	4/2003 Koch et al.			
8,722,021 B2	5/2014 Eini et al.		2003/0072760 A1	4/2003 Sirbasku			
8,734,846 B2	5/2014 Hrkach et al.		2003/0073248 A1	4/2003 Roth et al.			
8,735,381 B2	5/2014 Podolski		2003/0073673 A1	4/2003 Hesch			
8,741,336 B2	6/2014 Dipierro et al.		2003/0077297 A1	4/2003 Chen et al.			
8,741,373 B2	6/2014 Rao et al.		2003/0078245 A1	4/2003 Bennink et al.			
8,753,661 B2	6/2014 Gassner et al.		2003/0091640 A1	5/2003 Ramanathan et al.			
8,784,882 B2	7/2014 Mattern		2003/0092691 A1	5/2003 Besse et al.			
8,846,648 B2 *	9/2014 Bernick	A61K 9/16	2003/0096012 A1	5/2003 Besse et al.			
		424/452	2003/0104048 A1	6/2003 Patel et al.			
8,846,649 B2 *	9/2014 Bernick	A61K 9/16	2003/0109507 A1	6/2003 Beckmann et al.			
		424/452	2003/0113268 A1	6/2003 Buenafae et al.			

US 10,675,288 B2

Page 6

(56)

References Cited

U.S. PATENT DOCUMENTS

2003/0114420 A1	6/2003	Salvati et al.	2005/0003003 A1	1/2005	Basu et al.
2003/0114430 A1	6/2003	MacLeod et al.	2005/0004088 A1	1/2005	Hesch
2003/0124182 A1	7/2003	Shojaei et al.	2005/0021009 A1	1/2005	Thumbeck et al.
2003/0124191 A1	7/2003	Besse et al.	2005/0025833 A1	2/2005	Aschkenasay et al.
2003/0130558 A1	7/2003	Massara et al.	2005/0031651 A1	2/2005	Gervais et al.
2003/0144258 A1	7/2003	Heil et al.	2005/0042173 A1	2/2005	Besse et al.
2003/0157157 A1	8/2003	Luo et al.	2005/0042268 A1	2/2005	Aschkenasay et al.
2003/0166509 A1	9/2003	Edwards et al.	2005/0048116 A1	3/2005	Straub et al.
2003/0170295 A1	9/2003	Yoon et al.	2005/0054991 A1	3/2005	Paterson et al.
2003/0175329 A1	9/2003	Mak et al.	2005/0079138 A1	4/2005	Chickering, III et al.
2003/0175333 A1	9/2003	Shefer et al.	2005/0085453 A1	4/2005	Govindarajan
2003/0180352 A1	9/2003	Patel et al.	2005/0101579 A1	5/2005	Shippen
2003/0181353 A1	9/2003	Nyce	2005/0113350 A1	5/2005	Duesterberg et al.
2003/0181728 A1	9/2003	Salvati et al.	2005/0118244 A1	6/2005	Theobild et al.
2003/0191096 A1	10/2003	Leonard et al.	2005/0118272 A1	6/2005	Besse et al.
2003/0195177 A1	10/2003	Leonard et al.	2005/0129756 A1	6/2005	Podhaisky et al.
2003/0215496 A1	11/2003	Patel et al.	2005/0152956 A1	7/2005	Dudley
2003/0219402 A1	11/2003	Rutter	2005/0153946 A1	7/2005	Hirsh et al.
2003/0220297 A1	11/2003	Berstein et al.	2005/0164977 A1	7/2005	Coelingh Bennink
2003/0224057 A1	12/2003	Martin-Letellier et al.	2005/0182105 A1	8/2005	Nirschl et al.
2003/0224059 A1	12/2003	Lerner et al.	2005/0186141 A1	8/2005	Gonda et al.
2003/0225047 A1	12/2003	Friedman et al.	2005/0187267 A1	8/2005	Hamann et al.
2003/0225048 A1	12/2003	Friedman et al.	2005/0192253 A1	9/2005	Salvati et al.
2003/0225050 A1	12/2003	Eichardt et al.	2005/0192310 A1	9/2005	Gavai et al.
2003/0228686 A1	12/2003	Klausner et al.	2005/0196434 A1	9/2005	Briere
2003/0229057 A1	12/2003	Caubel et al.	2005/0207990 A1	9/2005	Funke et al.
2003/0235596 A1	12/2003	Gao et al.	2005/0209209 A1	9/2005	Koch et al.
2003/0236236 A1*	12/2003	Chen	A61B 17/0483	9/2005	Juturu et al.
			514/171	10/2005	Funke et al.
				10/2005	Wuttke et al.
2004/0009960 A1	1/2004	Heil et al.	2005/0220900 A1	10/2005	Bracht
2004/0022820 A1	2/2004	Anderson	2005/0222106 A1	10/2005	Hodgdon
2004/0034001 A1	2/2004	Karara	2005/0228692 A1	10/2005	Austin
2004/0037881 A1	2/2004	Guitard et al.	2005/0228718 A1	10/2005	Le et al.
2004/0039356 A1	2/2004	Maki et al.	2005/0239747 A1	10/2005	Roby
2004/0043043 A1	3/2004	Schlyter et al.	2005/0239758 A1	10/2005	Billoni
2004/0043943 A1	3/2004	Guitard et al.	2005/0244360 A1	11/2005	Carrara et al.
2004/0044080 A1	3/2004	Place et al.	2005/0244522 A1	11/2005	Cornish et al.
2004/0048900 A1	3/2004	Flood	2005/0245902 A1	11/2005	Iammatteo
2004/0052824 A1	3/2004	Abou Chakra-Vernet et al.	2005/0250746 A1	11/2005	Cummings et al.
2004/0073024 A1	4/2004	Metcalf, III et al.	2005/0250750 A1	11/2005	Fink et al.
2004/0077605 A1	4/2004	Salvati et al.	2005/0250753 A1	11/2005	Yun et al.
2004/0077606 A1	4/2004	Salvati et al.	2005/0256028 A1	11/2005	Jorda et al.
2004/0087548 A1	5/2004	Salvati et al.	2005/0266078 A1	12/2005	Frijlink et al.
2004/0087564 A1	5/2004	Wright et al.	2005/0266088 A1	12/2005	Keith
2004/0089308 A1	5/2004	Welch	2005/0271597 A1	12/2005	Friedman et al.
2004/0092494 A9	5/2004	Dudley	2005/0271598 A1	12/2005	Hung
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0272685 A1	12/2005	Grubb et al.
2004/0093261 A1	5/2004	Jain et al.	2005/0272712 A1	12/2005	Salvati et al.
2004/0097468 A1	5/2004	Wimalawansa	2006/0009428 A1	1/2006	Chwalisz et al.
2004/0101557 A1	5/2004	Gibson et al.	2006/0014728 A1	1/2006	Friedman et al.
2004/0106542 A1	6/2004	Deaver et al.	2006/0018937 A1	1/2006	Balog
2004/0110732 A1	6/2004	Masini et al.	2006/0019978 A1	1/2006	Fensome et al.
2004/0131670 A1	7/2004	Gao	2006/0020002 A1	1/2006	Jo et al.
2004/0138103 A1	7/2004	Patt	2006/0030615 A1	2/2006	Weimann
2004/0142012 A1	7/2004	Bunt et al.	2006/0034889 A1	2/2006	Ahmed et al.
2004/0146539 A1	7/2004	Gupta	2006/0034904 A1	2/2006	Dvoskin et al.
2004/0146894 A1	7/2004	Warrington et al.	2006/0040904 A1	2/2006	Cornish et al.
2004/0147578 A1	7/2004	Calvet	2006/0051391 A1	3/2006	Loumaye
2004/0161435 A1	8/2004	Gupta	2006/0052341 A1	3/2006	Constantinides et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0069031 A1	4/2006	Allison et al.
2004/0176336 A1	9/2004	Rodriguez	2006/0078618 A1	4/2006	Shih et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0083778 A1	4/2006	Seibertz et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0084704 A1	4/2006	Casper et al.
2004/0191276 A1	9/2004	Muni	2006/0088580 A1	4/2006	Chickering, III et al.
2004/0198706 A1	10/2004	Carrara et al.	2006/0089337 A1	4/2006	Bohlmann et al.
2004/0210280 A1	10/2004	Liedtke	2006/0093678 A1	5/2006	Brody et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0100180 A1	5/2006	Gupta
2004/0219124 A1	11/2004	Gupta	2006/0106004 A1	5/2006	Salvati et al.
2004/0225140 A1	11/2004	Sciano et al.	2006/0110415 A1	5/2006	Levine et al.
2004/0234606 A1	11/2004	Hille et al.	2006/0111424 A1	5/2006	Waldon et al.
2004/0241219 A1	12/2004	Grace et al.	2006/0121102 A1	6/2006	Netke et al.
2004/0243437 A1	12/2004	Grace et al.	2006/0121626 A1	6/2006	Anyarambhatla et al.
2004/0253319 A1	12/2004	Netke et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2004/0259817 A1	12/2004	Waldon et al.	2006/0135619 A1	6/2006	Kick et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0165744 A1	7/2006	Chiang

US 10,675,288 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2006/0193789 A1	8/2006	Tamarkin et al.	2008/0026035 A1	1/2008	Chollet et al.
2006/0194775 A1	8/2006	Tofovic et al.	2008/0026040 A1	1/2008	Rivera et al.
2006/0204557 A1	9/2006	Gupta et al.	2008/0026062 A1	1/2008	Farr et al.
2006/0233743 A1	10/2006	Kelly	2008/0038219 A1	2/2008	Carlson et al.
2006/0233841 A1	10/2006	Pushpala et al.	2008/0038350 A1	2/2008	Gerecke et al.
2006/0235037 A1	10/2006	Purandare et al.	2008/0039405 A1	2/2008	Joseph et al.
2006/0240111 A1	10/2006	Fernandez et al.	2008/0050317 A1	2/2008	Besonov et al.
2006/0246122 A1	11/2006	Langguth et al.	2008/0051351 A1	2/2008	Ghisalberti
2006/0247216 A1	11/2006	Haj-Yehia	2008/0063607 A1	3/2008	Berman et al.
2006/0247221 A1	11/2006	Coelingh et al.	2008/0069779 A1	3/2008	Schuz et al.
2006/0251581 A1	11/2006	Madenjian et al.	2008/0069791 A1	3/2008	Beissert
2006/0252049 A1	11/2006	Shuler et al.	2008/0085877 A1	4/2008	Bortz
2006/0257472 A1	11/2006	Neilsen	2008/0095831 A1	4/2008	Mc Graw
2006/0275218 A1	12/2006	Besonov et al.	2008/0095838 A1	4/2008	Abou Chacra-Vernet
2006/0275360 A1	12/2006	Ahmed et al.	2008/0119537 A1	5/2008	Zhang et al.
2006/0276414 A1	12/2006	Coelingh et al.	2008/0125402 A1	5/2008	Dilberti
2006/0280771 A1	12/2006	Groenewegen et al.	2008/0138379 A1	6/2008	Jennings-Spring
2006/0280797 A1	12/2006	Shoichet et al.	2008/0138390 A1	6/2008	Gricenko et al.
2006/0280800 A1	12/2006	Nagi et al.	2008/0139392 A1	6/2008	Yuan et al.
2006/0292223 A1	12/2006	Mc Ilroy et al.	2008/0145423 A1	6/2008	Khan et al.
2007/0004693 A1	1/2007	Woolfson et al.	2008/0153789 A1	6/2008	Dmowski et al.
2007/0004694 A1	1/2007	Woolfson et al.	2008/0175814 A1	7/2008	Phasivongsa et al.
2007/0009559 A1	1/2007	Alosio et al.	2008/0175905 A1	7/2008	Biksh et al.
2007/0009594 A1	1/2007	Grubb et al.	2008/0175908 A1	7/2008	Biksh et al.
2007/0010550 A1	1/2007	McKenzie	2008/0188829 A1	8/2008	Creasy
2007/0014839 A1	1/2007	Bracht	2008/0206156 A1	8/2008	Cronk
2007/0015698 A1	1/2007	Goldstein et al.	2008/0206159 A1	8/2008	Schuz et al.
2007/0021360 A1	1/2007	Nyce et al.	2008/0206161 A1	8/2008	Tamarkin et al.
2007/0027201 A1	2/2007	McComas et al.	2008/0214512 A1	9/2008	Seitz et al.
2007/0031491 A1	2/2007	Levine et al.	2008/0220069 A1	9/2008	Allison
2007/0036843 A1	2/2007	Hirsh et al.	2008/0226698 A1	9/2008	Beste et al.
2007/0037780 A1	2/2007	Anigbogu et al.	2008/0227763 A1	9/2008	Paris et al.
2007/0037782 A1	2/2007	Suzuki et al.	2008/0234199 A1	9/2008	Katamreddy
2007/0042038 A1	2/2007	Besse	2008/0234240 A1	9/2008	Duesterberg et al.
2007/0060589 A1	3/2007	Purandare et al.	2008/0255078 A1	10/2008	Katamreddy
2007/0066628 A1	3/2007	Zhang et al.	2008/0255089 A1	10/2008	Katamreddy
2007/0066637 A1	3/2007	Zhang et al.	2008/0261931 A1	10/2008	Stenlof et al.
2007/0066675 A1	3/2007	Zhang et al.	2008/0113953 A1	12/2008	DeVries et al.
2007/0071777 A1	3/2007	Bromer et al.	2008/0114050 A1	12/2008	Fensome et al.
2007/0078091 A1	4/2007	Hubler et al.	2008/0299220 A1	12/2008	Tamarkin et al.
2007/0088029 A1	4/2007	Balog et al.	2008/0306036 A1	12/2008	Katamreddy
2007/0093548 A1	4/2007	Diffendal et al.	2008/0312197 A1	12/2008	Rodriguez
2007/0116729 A1	5/2007	Palepu	2008/0312198 A1	12/2008	Rodriguez
2007/0116829 A1	5/2007	Prakash et al.	2008/0319078 A1	12/2008	Katamreddy
2007/0128263 A1	6/2007	Wall et al.	2009/0004246 A1	1/2009	Woolfson et al.
2007/0154533 A1	7/2007	Dudley	2009/0010968 A1	1/2009	Peyrot et al.
2007/0167418 A1	7/2007	Ferguson	2009/0011041 A1	1/2009	Musaeva et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0017120 A1	1/2009	Brisco et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0022683 A1	1/2009	Park et al.
2007/0185068 A1	8/2007	Ferguson et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0190022 A1	8/2007	Chia et al.	2009/0053294 A1	2/2009	Prendergast
2007/0191319 A1	8/2007	Ke et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0191321 A1	8/2007	Ahmed et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0196415 A1	8/2007	Houston et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196433 A1	8/2007	Ron et al.	2009/0074859 A1	3/2009	Patel
2007/0207225 A1	9/2007	Squadrito	2009/0081206 A1	3/2009	Leibovitz
2007/0225281 A1	9/2007	Zhang et al.	2009/0081278 A1	3/2009	De Graaff et al.
2007/0232574 A1	10/2007	Bernard et al.	2009/0081303 A1	3/2009	Savoir et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0243229 A1	10/2007	Smith et al.	2009/0093440 A1	4/2009	Murad
2007/0248658 A1	10/2007	Bracht et al.	2009/0098069 A1	4/2009	Vacca
2007/0254858 A1	11/2007	Cronk	2009/0099106 A1	4/2009	Phasivongsa et al.
2007/0255197 A1	11/2007	Wilkins et al.	2009/0099149 A1	4/2009	Kresevic
2007/0264309 A1	11/2007	Chollet et al.	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0264345 A1	11/2007	Eros et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0264349 A1	11/2007	Lee et al.	2009/0136574 A1	5/2009	Diaz-Astruc et al.
2007/0270394 A1	11/2007	El-Alfy et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0286819 A1	12/2007	DeVries et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0287688 A1	12/2007	Chan et al.	2009/0143344 A1	6/2009	Chang
2007/0287789 A1	12/2007	Jones et al.	2009/0164341 A1	6/2009	Sunvold et al.
2007/0292359 A1	12/2007	Schuz et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0181088 A1	7/2009	Song et al.
2007/0292461 A1	12/2007	Danziger et al.	2009/0186081 A1	7/2009	Slot et al.
2007/0292493 A1	12/2007	Briere	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0298089 A1	12/2007	Yoshinaga et al.	2009/0203658 A1	8/2009	Rose et al.
			2009/0214474 A1	8/2009	Jennings
			2009/0227025 A1	9/2009	Nichols et al.
			2009/0227550 A1	9/2009	Mattern
			2009/0232897 A1	9/2009	Sahoo et al.

US 10,675,288 B2

Page 8

(56)

References Cited

U.S. PATENT DOCUMENTS

2009/0258096 A1	10/2009	Cohen	2011/0195114 A1	8/2011	Carrara et al.
2009/0264395 A1	10/2009	Creasy	2011/0195944 A1	8/2011	Mura et al.
2009/0269403 A1	10/2009	Shaked et al.	2011/0217341 A1	9/2011	Sah
2009/0285772 A1	11/2009	Phasivongsa et al.	2011/0238003 A1	9/2011	Karabelas et al.
2009/0285869 A1	11/2009	Trimble	2011/0244043 A1	10/2011	Wang et al.
2009/0318558 A1	12/2009	Kim et al.	2011/0250256 A1	10/2011	Hyun et al.
2009/0324714 A1	12/2009	Kresevic et al.	2011/0250259 A1	10/2011	Buckman
2009/0325916 A1	12/2009	Zhang et al.	2011/0250274 A1	10/2011	Shaked et al.
2010/0008985 A1	1/2010	Vermeulen et al.	2011/0256092 A1	10/2011	Phasivongsa
2010/0028360 A1	2/2010	Atwood	2011/0262373 A1	10/2011	Umbert
2010/0034838 A1	2/2010	Staniforth et al.	2011/0262494 A1	10/2011	Achleitner et al.
2010/0034880 A1	2/2010	Sintov	2011/0268665 A1	11/2011	Tamarkin et al.
2010/0040671 A1	2/2010	Ahmed et al.	2011/0275584 A1	11/2011	Volkmann et al.
2010/0048523 A1	2/2010	Bachman et al.	2011/0281832 A1	11/2011	Wennogle et al.
2010/0055138 A1	3/2010	Jacobs et al.	2011/0287094 A1	11/2011	Penhasi et al.
2010/0074959 A1	3/2010	Hansom et al.	2011/0293720 A1	12/2011	General et al.
2010/0086501 A1	4/2010	Chang et al.	2011/0294738 A1	12/2011	Kuliopoulos et al.
2010/0086599 A1	4/2010	Huempel et al.	2011/0300167 A1	12/2011	Covic et al.
2010/0092568 A1	4/2010	Lerner et al.	2011/0301087 A1	12/2011	McBride et al.
2010/0105071 A1	4/2010	Laufer et al.	2011/0306579 A1	12/2011	Stein
2010/0119585 A1	5/2010	Hille et al.	2011/0311592 A1	12/2011	Birbara
2010/0129320 A1	5/2010	Phasivongsa et al.	2011/0312927 A1	12/2011	Nachaegari et al.
2010/0136105 A1	6/2010	Chen et al.	2011/0312928 A1	12/2011	Nachaegari et al.
2010/0137265 A1	6/2010	Leonard	2011/0318405 A1	12/2011	Erwin
2010/0137271 A1	6/2010	Chen et al.	2011/0318431 A1	12/2011	Gulati
2010/0143420 A1	6/2010	Lee et al.	2012/0009276 A1	1/2012	De Groote
2010/0143481 A1	6/2010	Shenoy et al.	2012/0015350 A1	1/2012	Nabatiyan et al.
2010/0150993 A1	6/2010	Theobald et al.	2012/0021041 A1	1/2012	Rossi et al.
2010/0152144 A1	6/2010	Hermsmeyer	2012/0028888 A1	2/2012	Janz et al.
2010/0168228 A1	7/2010	Bose et al.	2012/0028910 A1	2/2012	Takruri et al.
2010/0183723 A1	7/2010	Laurent-Applegate et al.	2012/0028936 A1	2/2012	Popova et al.
2010/0184736 A1	7/2010	Coelingh Bennink et al.	2012/0045532 A1	2/2012	Cohen
2010/0190758 A1	7/2010	Fauser et al.	2012/0046264 A1	2/2012	Lieb et al.
2010/0204326 A1	8/2010	D Souza	2012/0046518 A1	2/2012	Yoakum et al.
2010/0210994 A1	8/2010	Zarif	2012/0052077 A1	3/2012	Truitt, III et al.
2010/0221195 A1	9/2010	Ziv et al.	2012/0058171 A1	3/2012	Zeeman et al.
2010/0227797 A1	9/2010	Danielsson et al.	2012/0058962 A1	3/2012	Sparrow et al.
2010/0240626 A1	9/2010	Kulkarni et al.	2012/0058979 A1	3/2012	Auspitz et al.
2010/0247482 A1	9/2010	Chen et al.	2012/0064135 A1	3/2012	Harms et al.
2010/0247632 A1	9/2010	Dong et al.	2012/0065179 A1	3/2012	Andersson
2010/0247635 A1	9/2010	Schmidt et al.	2012/0065221 A1	3/2012	Babul
2010/0255085 A1*	10/2010	Liu	2012/0087872 A1	4/2012	Schuz et al.
		A61K 9/4858	2012/0101073 A1	4/2012	Mannion
		424/456	2012/0121517 A1	5/2012	Kim et al.
			2012/0121692 A1	5/2012	Fang et al.
			2012/0122829 A1	5/2012	Masini et al.
			2012/0128625 A1	5/2012	Shalwitz et al.
2010/0273730 A1	10/2010	Hsu et al.	2012/0128654 A1	5/2012	Terpstra et al.
2010/0278759 A1	11/2010	Murad	2012/0128683 A1	5/2012	Shantha
2010/0279988 A1	11/2010	Setiawan et al.	2012/0128733 A1	5/2012	Perrin et al.
2010/0291191 A1	11/2010	Lapitsky et al.	2012/0128777 A1	5/2012	Keck et al.
2010/0292199 A1	11/2010	Leverd et al.	2012/0129773 A1	5/2012	Geier et al.
2010/0303825 A9	12/2010	Sirbasku	2012/0129819 A1	5/2012	Vancaillie et al.
2010/0312137 A1	12/2010	Gilmour et al.	2012/0136013 A1	5/2012	Wennogle et al.
2010/0316724 A1	12/2010	Whitfield et al.	2012/0142645 A1	6/2012	Marx
2010/0322884 A1	12/2010	Wilkins et al.	2012/0148670 A1	6/2012	Lee et al.
2010/0330168 A1	12/2010	Gicquel et al.	2012/0149748 A1	6/2012	Shanler et al.
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0172343 A1	7/2012	Schuermann et al.
2011/0039814 A1	2/2011	Ross et al.	2012/0184515 A1	7/2012	Schwede et al.
2011/0053845 A1	3/2011	Levine et al.	2012/0231052 A1	9/2012	Brinton et al.
2011/0066473 A1	3/2011	Bernick et al.	2012/0232011 A1	9/2012	Kneissel et al.
2011/0076775 A1	3/2011	Stewart et al.	2012/0232042 A1	9/2012	Krenz et al.
2011/0076776 A1	3/2011	Stewart et al.	2012/0263679 A1	10/2012	Wallace et al.
2011/0086825 A1	4/2011	Chatroux	2012/0269721 A1	10/2012	Weng et al.
2011/0087192 A1	4/2011	Uhland et al.	2012/0277249 A1	11/2012	Tarrant et al.
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0277727 A1	11/2012	Doshi et al.
2011/0098258 A1	4/2011	Canet et al.	2012/0283671 A1	11/2012	Shibata et al.
2011/0098631 A1	4/2011	McIntyre et al.	2012/0295911 A1	11/2012	Mannion et al.
2011/0104268 A1	5/2011	Segot et al.	2012/0301517 A1	11/2012	Warner et al.
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	2012/0301538 A1	11/2012	Latere et al.
2011/0130372 A1	6/2011	Marliani et al.	2012/0302535 A1	11/2012	Caufriez et al.
2011/0135719 A1	6/2011	Besins et al.	2012/0316130 A1	12/2012	Hendrix
2011/0142945 A1	6/2011	Chen et al.	2012/0316496 A1	12/2012	Horres et al.
2011/0152840 A1	6/2011	Lee et al.	2012/0321579 A1	12/2012	Edelson et al.
2011/0158920 A1	6/2011	Fisher et al.	2012/0322779 A9	12/2012	Voskuhl
2011/0171140 A1	7/2011	Illum et al.	2012/0328549 A1	12/2012	Edelson et al.
2011/0182997 A1	7/2011	Lewis et al.	2012/0329738 A1	12/2012	Liu
2011/0190201 A1	8/2011	Wood, Jr. et al.	2013/0004619 A1	1/2013	Goh et al.
2011/0195031 A1	8/2011	Du	2013/0011342 A1	1/2013	Hazot et al.

US 10,675,288 B2

Page 9

(56)	References Cited				
U.S. PATENT DOCUMENTS					
2013/0017239 A1	1/2013 Fernandez et al.	2014/0088058 A1	3/2014 Maurizio		
2013/0022674 A1	1/2013 Dudley et al.	2014/0088059 A1	3/2014 Santha et al.		
2013/0023505 A1	1/2013 Garfield et al.	2014/0094426 A1	4/2014 Drummond et al.		
2013/0023823 A1	1/2013 Volland et al.	2014/0094440 A1	4/2014 Bernick et al.		
2013/0028850 A1	1/2013 Hazot et al.	2014/0094441 A1	4/2014 Bernick et al.		
2013/0029947 A1	1/2013 Nachaegari et al.	2014/0099362 A1	4/2014 Bernick et al.		
2013/0029957 A1	1/2013 Venkateshwaran et al.	2014/0100159 A1	4/2014 Conrad		
2013/0045266 A1	2/2013 Kang et al.	2014/0100204 A1	4/2014 Bernick et al.		
2013/0045953 A1	2/2013 Grenier et al.	2014/0100205 A1	4/2014 Bernick et al.		
2013/0059795 A1	3/2013 Lo et al.	2014/0100206 A1	4/2014 Cacace et al.		
2013/0064897 A1	3/2013 Binay	2014/0113889 A1	4/2014 Haine et al.		
2013/0072466 A1	3/2013 Choi et al.	2014/0127185 A1	5/2014 Sayeed et al.		
2013/0084257 A1	4/2013 Ishida et al.	2014/0127280 A1	5/2014 Jukarainen et al.		
2013/0085123 A1	4/2013 Zhao et al.	2014/0127308 A1	5/2014 Opara et al.		
2013/0089574 A1	4/2013 Stock et al.	2014/0128798 A1	5/2014 Malanchin et al.		
2013/0090318 A1	4/2013 Gainer et al.	2014/0148491 A1	5/2014 Valia et al.		
2013/0102781 A1	4/2013 Ely et al.	2014/0186332 A1	7/2014 Ezrin et al.		
2013/0108551 A1	5/2013 Gruell et al.	2014/0187487 A1	7/2014 Shoichet et al.		
2013/0116215 A1	5/2013 Leo et al.	2014/0193523 A1	7/2014 Henry		
2013/0116222 A1	5/2013 Altomari et al.	2014/0194396 A1	7/2014 Wennogle et al.		
2013/0122051 A1	5/2013 Gullapalli et al.	2014/0206616 A1	7/2014 Ko et al.		
2013/0123175 A1	5/2013 McKee et al.	2014/0213565 A1	7/2014 Bernick et al.		
2013/0123220 A1	5/2013 Queiroz	2014/0329783 A1	11/2014 Bernick et al.		
2013/0123351 A1	5/2013 Dewitt	2014/0370084 A1	12/2014 Bernick et al.		
2013/0129818 A1	5/2013 Bernick et al.	2014/0371182 A1	12/2014 Bernick et al.		
2013/0131027 A1	5/2013 Schmitz et al.	2014/0371183 A1	12/2014 Bernick et al.		
2013/0131028 A1	5/2013 Snyder et al.	2014/0371184 A1	12/2014 Bernick et al.		
2013/0131029 A1	5/2013 Baltussen et al.	2014/0371185 A1	12/2014 Bernick et al.		
2013/0149314 A1	6/2013 Bullerdiek et al.	2015/0031654 A1	1/2015 Amadio		
2013/0164225 A1	6/2013 Besonov et al.	2015/0045335 A1	2/2015 Bernick et al.		
2013/0164346 A1	6/2013 Son et al.	2015/0133421 A1	5/2015 Bernick et al.		
2013/0165744 A1	6/2013 Carson et al.	2015/0148323 A1	5/2015 Bernick et al.		
2013/0178452 A1	7/2013 King	2015/0164789 A1	6/2015 Bernick et al.		
2013/0183254 A1	7/2013 Cochran et al.	2015/0224117 A1	8/2015 Bernick et al.		
2013/0183325 A1	7/2013 Sforzini et al.	2015/0224118 A1	8/2015 Bernick et al.		
2013/0189193 A1	7/2013 Besonov et al.	2015/0297733 A1	10/2015 Oberegger et al.		
2013/0189196 A1	7/2013 Tamarkin et al.	2015/0302435 A1	10/2015 Bernick et al.		
2013/0189230 A1	7/2013 Kooy et al.	2015/0342963 A1	12/2015 Bernick et al.		
2013/0189368 A1	7/2013 Mosqueira et al.	2015/0351226 A1	12/2015 Bernick et al.		
2013/0210709 A1	8/2013 Covis et al.	2015/0359737 A1	12/2015 Bernick et al.		
2013/0216550 A1	8/2013 Penninger et al.	2016/0030449 A1	2/2016 Persicaner et al.		
2013/0216596 A1	8/2013 Fernandez et al.	2016/0213685 A1	7/2016 Bernick et al.		
2013/0224177 A1	8/2013 Kim et al.	2017/0056418 A1	3/2017 Thorsteinsson et al.		
2013/0224257 A1	8/2013 Sah et al.	2017/0216310 A1	8/2017 Mirkin et al.		
2013/0224268 A1	8/2013 Jaikaria et al.	2017/0281645 A1	10/2017 Shadiack et al.		
2013/0224300 A1	8/2013 Maggio	2017/0281646 A1	10/2017 Inskeep et al.		
2013/0225412 A1	8/2013 Sardari et al.	2017/0281647 A1	10/2017 Shadiack et al.		
2013/0225542 A1	8/2013 Frick et al.	2017/0281776 A1	10/2017 Shadiack et al.		
2013/0226113 A1	8/2013 Langguth et al.	2018/0161343 A1	6/2018 Mirkin et al.		
2013/0243696 A1	9/2013 Wang et al.	2018/0161345 A1	6/2018 Bernick et al.		
2013/0245253 A1	9/2013 Mook et al.	2018/0221389 A1	8/2018 Amadio et al.		
2013/0245570 A1	9/2013 Jackson	FOREIGN PATENT DOCUMENTS			
2013/0261096 A1	10/2013 Merian et al.	CA 2612380	12/2006		
2013/0266645 A1	10/2013 Schoenecker et al.	CN 102258455 A	11/2011		
2013/0267485 A1	10/2013 Da Silva	EP 0261429 A1	3/1988		
2013/0273167 A1	10/2013 Kim et al.	EP 0275716 A1	7/1988		
2013/0274211 A1	10/2013 Prusthy et al.	EP 0279977 A2	8/1988		
2013/0280213 A1	10/2013 Voskuhl	EP 0622075 A1	11/1994		
2013/0316374 A1	11/2013 Menon et al.	EP 0785211 A1	7/1997		
2013/0317065 A1	11/2013 Seto et al.	EP 0785212 A1	7/1997		
2013/0317315 A1	11/2013 Tsang et al.	EP 0811381 A1	12/1997		
2013/0324565 A1	12/2013 Zhao et al.	EP 0904064 A1	3/1999		
2013/0331363 A1	12/2013 Zhao et al.	EP 0813412 B1	12/1999		
2013/0338122 A1	12/2013 Bernick et al.	EP 0750495 B1	12/2002		
2013/0338123 A1	12/2013 Bernick et al.	EP 1300152 A1	4/2003		
2013/0338124 A1	12/2013 Zhao et al.	EP 1094781 B1	7/2008		
2013/0345187 A1	12/2013 Rodriguez	EP 2191833 A1	6/2010		
2014/0018335 A1	1/2014 Seto et al.	GB 452238 A	8/1936		
2014/0024590 A1	1/2014 Taylor et al.	GB 720561 A	12/1954		
2014/0031289 A1	1/2014 Kim et al.	GB 848881 A	9/1960		
2014/0031323 A1	1/2014 Perez	GB 874368 A	8/1961		
2014/0066416 A1	3/2014 Leunis et al.	GB 1589946 A	5/1981		
2014/0072531 A1	3/2014 Oh et al.	IN 2005KOL00053	8/2005		
2014/0079686 A1	3/2014 Prouty et al.	IN 216026	3/2008		
2014/0088051 A1	3/2014 Bernick et al.	IN 244217	11/2010		
		JP H4-503810	9/1990		

US 10,675,288 B2

Page 10

(56)	References Cited				
	FOREIGN PATENT DOCUMENTS				
JP	H2-264725 A 10/1990	WO	2005087199	9/2005	
JP	H 10-251116 A 9/1998	WO	2005105059	11/2005	
JP	2002 510336 A 4/2002	WO	2005115335	12/2005	
JP	2006 513182 A 4/2006	WO	2005120470	12/2005	
RU	2155582 C2 9/2000	WO	2005120517	12/2005	
RU	2449796 C2 2/2006	WO	2006013369	2/2006	
WO	199010425 A1 9/1990	WO	2006034090	3/2006	
WO	1990011064 10/1990	WO	2006036899	4/2006	
WO	1993017686 9/1993	WO	2006053172	5/2006	
WO	1994022426 10/1994	WO	2006105615	10/2006	
WO	1995005807 3/1995	WO	2006113505	10/2006	
WO	1995030409 11/1995	WO	2006138686	12/2006	
WO	1996009826 4/1996	WO	2006138735	12/2006	
WO	1996019975 7/1996	WO	2007045027	4/2007	
WO	1996030000 10/1996	WO	2007076144 A2	7/2007	
WO	1997005491 2/1997	WO	2007103294	9/2007	
WO	1997043989 11/1997	WO	2007120868	10/2007	
WO	1998010293 3/1998	WO	2007123790	11/2007	
WO	1998032465 7/1998	WO	2007124250	11/2007	
WO	1998041217 A1 9/1998	WO	2007144151	12/2007	
WO	1998051280 11/1998	WO	2008049516	5/2008	
WO	1999022680 A1 5/1999	WO	2008152444	12/2008	
WO	1999032072 7/1999	WO	2009002542	12/2008	
WO	1999039700 8/1999	WO	2009036311	3/2009	
WO	1999042109 8/1999	WO	2009040818	4/2009	
WO	1999043304 9/1999	WO	2009069006	6/2009	
WO	1999048477 9/1999	WO	2009098072	8/2009	
WO	1999052528 A1 10/1999	WO	2009133352	11/2009	
WO	1999053910 10/1999	WO	2010033188	3/2010	
WO	1999055333 A1 11/1999	WO	2010146872	12/2010	
WO	1999062497 A1 12/1999	WO	2011000210	1/2011	
WO	1999063974 12/1999	WO	2011073995	6/2011	
WO	2000001351 1/2000	WO	2011120084	10/2011	
WO	2000006175 2/2000	WO	2011128336	10/2011	
WO	2000038659 6/2000	WO	2012009778	1/2012	
WO	2000045795 8/2000	WO	2012024361	2/2012	
WO	2000050007 8/2000	WO	2012055814 A1	5/2012	
WO	2000059577 10/2000	WO	2012055840 A1	5/2012	
WO	2000076522 12/2000	WO	2012065740	5/2012	
WO	2001037808 5/2001	WO	2012098090 A1	7/2012	
WO	2001054699 8/2001	WO	2012116277 A1	8/2012	
WO	2001060325 8/2001	WO	2012118563 A2	9/2012	
WO	2001087276 11/2001	WO	2012120365 A1	9/2012	
WO	2001091757 12/2001	WO	2012127501 A2	9/2012	
WO	2002007700 1/2002	WO	2012156561 A1	11/2012	
WO	2002011768 2/2002	WO	2012156822 A1	11/2012	
WO	2002022132 3/2002	WO	2012158483 A2	11/2012	
WO	2002040008 5/2002	WO	2012166909 A1	12/2012	
WO	2002041878 5/2002	WO	2012170578 A1	12/2012	
WO	2002053131 7/2002	WO	2013011501 A1	1/2013	
WO	2002078602 10/2002	WO	2013025449 A1	2/2013	
WO	2002078604 10/2002	WO	2013028639 A1	2/2013	
WO	2003028667 4/2003	WO	2013035101 A1	3/2013	
WO	2003041718 5/2003	WO	2013044067 A1	3/2013	
WO	2003041741 5/2003	WO	2013045404 A2	4/2013	
WO	2003068186 8/2003	WO	2013059285 A1	4/2013	
WO	2003077923 9/2003	WO	2013063279 A1	5/2013	
WO	2003082254 10/2003	WO	2013064620 A1	5/2013	
WO	2003092588 11/2003	WO	2013071281 A1	5/2013	
WO	2004014397 A1 2/2004	WO	2013078422 A2	5/2013	
WO	2004014432 2/2004	WO	2013088254	6/2013	
WO	2004017983 3/2004	WO	2013102665 A1	7/2013	
WO	2004032897 4/2004	WO	2013106437 A1	7/2013	
WO	2004032942 A1 4/2004	WO	2013112947 A1	8/2013	
WO	2004052336 6/2004	WO	2013113690	8/2013	
WO	2004054540 7/2004	WO	2013124415 A1	8/2013	
WO	2004054576 A1 7/2004	WO	2013127727 A1	9/2013	
WO	2004080413 9/2004	WO	2013127728 A1	9/2013	
WO	2004105694 A2 12/2004	WO	2013144356 A1	10/2013	
WO	2004110402 A1 12/2004	WO	2013149258 A2	10/2013	
WO	2004110408 A2 12/2004	WO	2013158454 A2	10/2013	
WO	2005027911 3/2005	WO	2013170052 A1	11/2013	
WO	2005030175 4/2005	WO	2013178587 A1	12/2013	
WO	2005081825 9/2005	WO	2013181449 A1	12/2013	
WO	2005087194 9/2005	WO	2013192248	12/2013	
		WO	2013192249	12/2013	
		WO	2013192250	12/2013	
		WO	2013192251	12/2013	
		WO	2014001904 A1	1/2014	

US 10,675,288 B2

Page 11

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2014004424	A1	1/2014
WO	2014009434	A1	1/2014
WO	2014018569	A1	1/2014
WO	2014018570	A1	1/2014
WO	2014018571	A2	1/2014
WO	2014018856	A1	1/2014
WO	2014018932	A2	1/2014
WO	2014031958	A1	2/2014
WO	2014041120	A1	3/2014
WO	2014052792	A1	4/2014
WO	2014056897	A1	4/2014
WO	2014066442	A2	5/2014
WO	2014074846	A1	5/2014
WO	2014076231	A1	5/2014
WO	2014076569	A2	5/2014
WO	2014081598	A1	5/2014
WO	2014086739	A1	6/2014
WO	2014093114	A1	6/2014
WO	2014104784	A1	7/2014
WO	2015179782	A1	11/2015
WO	2016018993	A1	2/2016

OTHER PUBLICATIONS

- Chambin et al., "Interest of Multifunctional Lipid Excipients: Case of Gelucire® 44/14," Drug Development and Industrial Pharmacy, vol. 31, No. 6, pp. 527-534 (Year: 2005).*
- Abbas et al., Regression of endometrial implants treated with vitamin D₃ in a rat model of endometriosis, European J of Pharma, 715 (2013) 72-75, Elsevier.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Acarturk, Fusun, Mucoadhesive Vaginal Drug Delivery System, Recent Patents on Drug Delivery & Formulation, 2009, vol. 3, pp. 193-195.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, Fountain Journal of Nat. and Appl. Sciences, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, Neuroscience, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceuticals substances—Steroids (2), Jasco International Co., Ltd., 2 pages.
- Araya-SIB1JA et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Araya-SIB1JA, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-SIB1JA, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-SIB1JA, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Araya-SIB1JA, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, Menopause: The Journal of the North American Menopause Society, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, Advances in Therapy®, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, Yale J Biology and Medicine, vol. 35, Feb. 1963, pp. 329-340.
- Azeem, Adnan et al., Microemulsions as a Surrogate Carrier for Dermal Drug Delivery, Drug Development and Industrial Pharmacy, May 2000, vol. 35, No. 5, pp. 525-547 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/0363904082448646>.
- Azure Pharma, Inc., Elestrin™—Estradiol Gel, Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, Aug. 2009.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, Current Medicinal Chemistry, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, Biology of Reproduction 52, 1327-1333 (1995).
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani Bhagu R. et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3):756-759.
- Bhavnani et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ERα and ERβ, Endocrinology, Oct. 2008, 149(10):4857-4870.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductiveaged female subjects, Fertility and Sterility# vol. 94, No. 4, Sep. 2010, Elsevier.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index> [Feb. 3, 2014 1:37:50 PM].
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiolophenylarsine)palladium(II).

US 10,675,288 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Molcculaire de la Progesterone C21H30O2, *Acta Cryst.*, B28 pp. 3032-3042, 1972.
- Castelo-Branco Camil et al., "Treatment of atrophic vaginitis," *Therapy*, 2007, vol. 4, No. 3, pp. 349-353.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Cho, Y.A. et al., Transdermal Delivery of Ketorolac Tromethamine: Effects of Vehicles and Penetration Enhancers, *Drug Development and Industrial Pharmacy*, 30(6):557-564, Jun. 2004.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, *J Clin Oncol* 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008: 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance , *Contact Dermatitis*, 71, 264-272, 2014.
- Chun et al., Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles . . . , *J. Kor. Pharm. Sci.*, vol. 35, No. 3, pp. 173-177 (2005).
- Cincinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, March 2000, pp. 403-406.
- Cincinelli et al., "First uterine pass effect" is observed when estradiol is placed in the upper but not lower third of the vagina, *Fertility and Sterility*, Vol. 81, No. 5, May 2004, pp. 1414-1416.
- Cincinelli, Intravaginal oestrogen and progestin administration: advantages and disadvantages, *Best Practices & Research Clinical Obstetrics and Gynaecology* vol. 22, No. 2, 2008, pp. 391-405.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, *Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div.*, vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Committee Opinion, Incidentally Detected Short Cervical Length, Committee of Obstetric Practice, *Obstetrics & Gynecology*, ACOG, vol. 119, No. 4, Apr. 2012, pp. 879-882.
- Commodari, Fernando, Comparison of 17 β -estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, *Research Letters*, Apr. 25, 1998.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," *Southern Medical Journal*, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Corn Refiners Association, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Crandall, Carolyn, "Vaginal Estrogen Preparations: A Review of Safety and Efficacy for Vaginal Atrophy," *Journal of Women's Health*, 2002, vol. 11, No. 10, pp. 857-877.
- Cremer Care, "Miglyol® 810, 812 INCI: Caprylic/Capric Triglyceride," Cremer Oleo GmbH & Co. KG, pp. 1-7, available at http://s3.amazonaws.com/petercremerna/products/spec_sheets/159/339/301/_original/M_IGL_YOL_81_0_812_TDS.pdf?1389204445 (Mar. 2013) accessed on Dec. 30, 2016.
- Critchley et al., Estrogen Receptor β , But Not Estrogen Receptor α , Is Present in the Vascular Endothelium of the Human and Non-human Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Diramio, Jackie A., Polyethylene Glycol Methacrylate/Dimethylacrylate Hydrogels for Controlled Release of Hydrophobic Drugs, Masters of Science Thesis, University of Georgia, Athens, Georgia, 2002, 131 pages.
- Drakulic, Branko J. Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *SciFinder, Pharmaceutica Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Estradiol, The Merck Index Online, Royal Society of Chemistry, <https://www.rsc.org/Merck-Index/monograph/mono1500003758/estradiol?q=unauthorize>.
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117. Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GMBH, 2010, 28 pages.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Brazil.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene B1sed on exposure and effect data, *Contact Dermatitis* 1990: 23: 341-345.
- Fotherby, K., Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, *Contraception*, 1996; 54:59-69.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.*(2013), Elsevier.
- Fuchs et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Cutis*. Jun. 2003;71(6):481-8.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.

US 10,675,288 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gäfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, British Journal of Dermatology 2002; 146: 649-656.
- Ganam-Quintanar et al., Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss, International Journal of Pharmaceutics, vo. 147, No. 2, Feb. 28, 1997, pp. 165-171 (abstract only).
- Garad S. et al., "Preclinical Development for Suspensions," A.K. Kulshreshtha et al. (eds.), *Pharmaceutical Suspensions: From Formulation Development to Manufacturing*, Springer, New York 2010, pp. 127-176.
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/B1ck-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," The Journal of Nutrition, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, Maturitas 19 (1994) 103-115.
- Giron-Forest, D. et al., Thermal analysis methods for pharmacopeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Giron-Forest, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochimica Acta, vol. 248 pp. 1-59, 1995, Elsevier.
- Glaser et al., Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, Gynecol Obstet Invest 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, Clinica Chimica Acta 419 (2013) 42-46.
- Graham et al., Physiological Action of Progesterone in Target Tissues, Endocrine Reviews, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, Human Reproduction Update, vol. 13, No. 4 pp. 405-417, 2007.
- Gunstone, Frank D. et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Gurney, E.P. et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats, International Journal of Pharmaceutics 379 (2009) 100-108, Elsevier.
- Haner, Barbara, Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hargrove et al., Menopausal Hormone Replacement Therapy with Continuous Daily Oral Micronize Estradiol and Progesterone, Obstet Gynecol, vol. 73, No. 4, Apr. 1989, pp. 606-612.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, Gynecol Obstet Invest 2013;76:51-56.
- Helbling, Ignacio M. et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, Clinic Pharmacol Biopharmaceut, 2014, S2, 7 pages.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Sturdy of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Herman, Anna et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, Journal of Pharmacy and Pharmacology, pp. 1-13.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Holm et al., "Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides," European Journal of Pharmaceutical Sciences 20 (2003) 91-97.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hostynk, JJ, Predicting absorption of fragrance chemicals through human skin, J. Soc.CosmeCt. hem., 4 6, 221-229 (Jul./Aug. 1, 1995).
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Humberstone, Andrew et al., "Lipid-based vehicles for the oral delivery of poorly water soluble drugs," Advanced Drug Delivery Reviews, 25 (1997) 103-128.
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, Journal of Cerebral Blood Flow and Metabolism 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 α -Ethynodiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 β -Estradiol, JPET 290(2):740-747, 1999.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johanson, Gunnar, Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester, Critical Reviews in Toxicology, 2000, vol. 30, No. 3, pp. 307-345 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/10408440091159220>.
- Johnson, William S. et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, J Reprod Fert (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, Environmental Health Perspectives • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karande, et al. Enhancement of transdermal drug delivery via synergistic action of chemicals, Biochimica et Biophysica Acta, 1788:2362-2373, Sep. 2009.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, Contact Dermatitis, 1992; 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, Ann. Occup. Hyg., vol. 38, No. 2, pp. 199-207, 1994.

US 10,675,288 B2

Page 14

(56)

References Cited

OTHER PUBLICATIONS

- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, B Izedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Kincl et al., Increasing Oral Bioavailability of Progesterone by Formylation, *Journal of Steroid Biochemistry*, 1978, vol. 9, pp. 83-84.
- Knuth et al., Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations, *Advanced Drug Delivery Reviews*, vol. 11, No. 1-2, Jul.-Aug. 1993, pp. 137-167.
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.
- Komm et al., B Izedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of The Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N. Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyniiewski, R., et al., EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C., et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier (abstract only).
- Kuhnert-Brandstaetter and Grimm. Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II, *Mikrochimica Acta*, vol. 1, pp. 127-139, 1968.
- Kuhnert-Brandstaetter and Junger and Kofler. Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Kuhnert-Brandstaetter and Kofler. Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, *Mikrochimica Acta*, vol. 6, pp. 847-853, 1959.
- Kuhnert-Brandstaetter and Linder. Zur Hydratbildung bei Steroidhormonen, *Sci. Pharm.*, vol. 41(2), pp. 109-116, 1973.
- Kumasaka et al., Effects of Various Forms of Progestin on the the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2), 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol*. Jul. 2011 ; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVV in OBGYN*, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol*. May 2010 ; 202(5): 455.e1-455.e9.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika. Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W., et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Lane, Majella E., "Skin penetration enhancers," *International Journal of Pharmaceutics* 447 (2013) 12-21.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- Leonetti, Helene B., et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G. et al., Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women, *Maturitas*, *The European Menopause Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lindmark, Tuulikki et al., "Absorption Enhancement through Intracellular Regulation of Tight Junction Permeability by Medium Chain Fatty Acids in Caco-2 Cells," *JPET* 284(1):362-369, 1998.
- Lindmark, Tuulikki et al., "Mechanisms of Absorption Enhancement by Medium Chain Fatty Acids in Intestinal Epithelial Caco-2 Cell Monolayers," *JPET* 275(2):958-964, 1995.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lopes, Luciana B. et al., Enhancement of transdermal delivery of progesterone using medium-chain mono and diglycerides as skin penetration enhancers, *Pharmaceutical Development and Technology*, 14:5, 524-529, Mar. 2009.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Lucy et al., Gonadotropin-releasing hormone at estrus: lutenizing hormone, estradiol, and progesterone during . . . *Biol Reprod* Sep. 1986;35(2):300-311 (abstract only).
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Mac Bride, Maire B. et al., "Vulvovaginal Atrophy," *Mayo Clin Proc*, Jan. 2010, 85(1):87-94.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Magness, R.R., et al., Estrone, Estradiol-17 β and Progesterone Concentrations in Uterine Lymph and Systematic Blood throughout the Porcine Estrone Estrous Cycle, *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- Martelli, Mary Elizabeth, "Vaginal Medicine Administration," *The Gale Encyclopedia of Nursing and Allied Health*, Gale Group, 2002, pp. 2542-2543.

US 10,675,288 B2

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(56)

References Cited

OTHER PUBLICATIONS

- McGuffey, Irena, Softgel Technology as a Lipid-B1sed Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Mesley, R.J., Clathrate Formation from Steroids, Chemistry and Industry, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration by Intramuscular and vaginal routes: a comparative study, Fertility and Sterility, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, Journal of Cancer Therapy, 2012, 3, 749-754.
- Monti, D. et al., Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin, International Journal of Pharmaceutics, 237:209-24, 2002.
- Mueck, A.O. et al., Genomic and non-genomic actions of progestogens in the breast, J. Steroid Biochem. Mol.Biol. (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone, J. Pharmaceutical Sciences, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Ng, Jo-Han et al., Advances in biodiesel fuel for application in compression ignition engines, Clean Techn Environ Policy, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , Drug Devel. & Indust. Pharmacy,35(9) pp. 1035, 2009.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, Chromatographia vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, Obstetrics & Gynecology, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- NuGen, What is NuGen HP Hair Growth System.
- NuGest900, NuGest 900™.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical application of pregersterone cream to pre-and post-menopausal women, Clinical Endocrinology, vol. 53 pp. 615-620, Blackwell Science 2000.
- Opinion on the Diethylene Glycol Monoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, n engl j med 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Pachman et al., "Management of menopause-associated vasomotor symptoms: current treatment options, challenges and future directions," International Journal of Women's Health, May 7, 2010.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, Pharmaceutical Technology Oct. 2004, pp. 74-88.
- Panay et al., The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy, Menopause International: The Integrated Journal of Postreproductive Health, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Panchangnula et al., Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol . . . , J Pharm Pharmacol. Sep. 1991;43(9):609-614 (abstract only).
- Parasuraman et al., Blood sample collection in small laboratory animals, Journal of Pharmacology & Pharmacotherapeutics | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, Arch Pharm Res, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , European Journal of Pharmaceutics and Biopharmaceutics, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, Crystal Structure Comm., Int'l Union of Crystallography, ISSN 0108-2701, 2003.
- Patel et al., Transdermal Drug Delivery System: A Review, www.thepharmajournal.com, vol. 1, No. 4, 2012, pp. 78-87.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, Intl. Jour. of Pharma., vol. 177 pp. 231-245, 1999, Elsevier.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pfau et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, PNAS, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, Br Med Journal, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? Menopause: The Journal of the North American Menopause Society, vol. 21, No. 12, 2014, pp. 1-3.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, Menopause, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Position Statement, Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society (NAMS), Menopause, vol. 20, No. 9, pp. 888-902.
- Potluri, Praveen and Gum V. Betageri, "Mixed-micellar proliposomal systems for enhanced oral delivery of progesterone," Drug Delivery, 2006, vol. 13, No. 3, pp. 227-232.
- Practice Bulletin No. 141, Management of Menopausal Symptoms, Obstetrics & Gynecology, ACOG, vol. 123, No. 1, Jan. 2014, pp. 202-216.
- Prajapati Hetal N. et al., "A Comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/ Water Phase Diagram, Solubility Determination and Dispersion Testing for Application in Pharmaceutical Dosage Form Development," Pharm Res. Jan. 2012; 29(1): 285-305. Published online Aug. 23, 2011. doi: 10.1007/s11095-011-0541-3.
- Prajapati Hetal N. et al., "Effect of Difference in Fatty Acid Chain Lengths of Medium-Chain Lipids on Lipid/Surfactant/Water Phase Diagrams and Drug Solubility," J. Excipients and Food Chem. 2 (3) 2011:73-88.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/ Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Prausnitz et al., Transdermal drug delivery, Nat Biotechnol. Nov. 2008 ; 26(11): 1261-1268.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, Adv. Drug Delivery Reviews, vol. 56 pp. 301-319, 2004, Elsevier.
- Product Information Sheet, Body B1llance Cream, Tahitian Noni International, 2013, 1 page.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Progesterone, The Merck Index Online, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index-monograph/print/mono1500007889/progesterone?q=authorize>.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.

US 10,675,288 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause A Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014, 6: 139-143.
- Rao, R. et al., "The Affect of Capmul, Labrafil and Transcutol on Progesterone 100 Mg Soft Capsules Bioavailability in Indian Healthy Adult Postmenopausal Female Subjects Under Fasting Conditions," *Bioequivalence & Bioavailability*, 7(2):095-107, 2015.
- Regidor, P., "Progesterone in Peri- and Postmenopause: A Review," *Geburtshilfe Frauenheilkd.* Nov. 2014 74(11):995-1002.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181, 512-520 (2014).
- Rosilio, V. et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *Ann J Obstet Gynecol.* Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010;5 943-954, Dove Press.
- Sallee, Verney L. et al., "Determinants of intestinal mucosal uptake of short- and medium-chain fatty acids and alcohols," *Journal of Lipid Research*, 1973, vol. 14, 475-484.
- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Salole, Eugene G., The physicochemical properties of oestradiol, *Journal of Pharmaceutical & Biomedical Analysis*, vol. 5, No. 7, pp. 635-648, 1987.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, *Climacteric* 2014;17:1-14.
- Sarkar, BISU, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ B1se . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Sarpal, K. et al., "Self emulsifying drug delivery systems: a strategy to improve oral bioavailability," *Current Research & Information on Pharmaceuticals Sciences (CRIPS)*, 2010, vol. 11, No. 3, pp. 42-49.
- Sarrel, et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, *American Journal of Public Health, Research and Practice*, e1-e6. Published online ahead of print Jul. 18, 2013.
- Satyanarayana, D. et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem.Mol. Biol.* (2013), Elsevier.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, *Maturitas* 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, *Fertil Steril.* Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, *Toxicologic Pathology*, 42: 1188-1196, 2014.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Search Report, Extended European Search Report for EP13741053. 6, dated Jul. 1, 2015.
- Search Report, Extended European Search Report for EP13807188. 1, dated Nov. 23, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US12/66406, dated Jan. 24, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/23309, dated Apr. 9, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46442, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46443, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46444, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46445, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US14/61811, dated Jan. 21, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/23041, dated Jun. 30, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/42621, dated Oct. 29, 2015.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, *Journal of Experimental & Clinical Cancer Research* 2014, 33(1):41, 11 pages.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *Journal of Adolescent Health*, 2003; 32:183-186.
- Shufelt et al., Hormone therapy dose, formulation, route delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 3, 2014, pp. 1-7, 2013.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, *Pharmaceutical Technology*, Aug. 2014, pp. 28, 30-31.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaproducts.com/catalog/product/sigma/p7556>.
- Simon et al., Effective Treatment of Vaginal atrophy with an Ultra-low-dose estradiol vaginal tablet, *Obstetrics & Gynecology*, vol. 112, No. 5, Nov. 2008, pp. 1053-1060.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware et al., Progestogens in hormonal replacement therapy: new molecules, risks, and benefits, *Menopause: The Journal of the North American Menopause Society*. vol. 9, No. 1, pp. 6-15, 2002.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," *Maturitas* 47 (2004) 277-283.
- Sitruk-Ware, Regine, Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review, *Contraception*, Oct. 1987, vol. 36, No. 4, pp. 373-402.
- Smith et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, *JAMA Internal Medicine*, Published online Sep. 30, 2013, E1-E7. jamainternalmedicine.com.
- Smyth et al., Summary of Toxicological Data, A 2-yr Study of Diethylene Glycol Monoethyl Ether in Rats, *Fd Cosmet. Toxicol.* vol. 2, pp. 641-642, 1964.

US 10,675,288 B2

Page 17

(56)

References Cited**OTHER PUBLICATIONS**

- Stanczyk et al., Therapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, *Contraception*, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause: The Journal of the North American Menopause Society*, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z. et al., Ethynodiol and 17 β -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, *Contraception* 87 (Jun. 2013) vol. 87, No. 6, pp. 706-727.
- Stanczyk, F.Z., "All progestins are not created equal," *Steroids* 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" *Climacteric* 2014;17 (Suppl 2):8-11.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," *Int J Pharmaceutical Compounding*, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Strickley, Robert T., Solubilizing excipients in oral and injectable formulations, *Pharmaceutical Research* Feb. 2004, vol. 21, Issue 2, pp. 201-230 (abstract only).
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- Struhar, M. et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, *Alternative Medicine Review* vol. 12, No. 3, 2007, pp. 259-264.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helveticae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, *Biology of Reproduction* 31, 399-413 (1984).
- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, *Gynecol Endocrinol*, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Thomas, Peter, Characteristics of membrane progestin receptor alpha (mPR α) and progesterone membrane receptor component 1 (PGMRC1) and their roles in mediating rapid progestin actions, *Frontiers in Neuroendocrinology* 29 (2008) 292-312.
- Tripathi, R. et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010.
- Trommer et al., Overcoming the stratum Corneum: The modulation of Skin Penetration, *Skin Pharmacol Physiol* 2006;19:106-121.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- Ueda et al., Topical and Transdermal Drug Products, *Pharmacopeial Forum*, vol. 35(3) [May-Jun. 2009], 750-754.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Certificate—Corn Oil, Lot G0L404, Jul. 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- U.S. Appl. No. 12/561,515, filed Dec. 12, 2011 Non-Final Office Action.
- U.S. Appl. No. 12/561,515, filed Oct. 26, 2012 Final Office Action.
- U.S. Appl. No. 12/561,515, filed Sep. 11, 2013 Notice of Allowance.
- U.S. Appl. No. 13/684,002, filed Mar. 20, 2013 Non-Final Office Action.
- U.S. Appl. No. 13/684,002, filed Jul. 16, 2013 Final Office Action.
- U.S. Appl. No. 13/684,002, filed Dec. 6, 2013 Notice of Allowance.
- U.S. Appl. No. 13/843,362, filed Mar. 16, 2015 Restriction Requirement.
- U.S. Appl. No. 13/843,428, filed Apr. 14, 2015 Restriction Requirement.
- U.S. Appl. No. 13/843,428, filed Jul. 2, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/099,545, filed Feb. 18, 2014_Non_Final_Offic Action.
- U.S. Appl. No. 14/099,545, filed Jul. 14, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,562, filed Feb. 20, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,562, filed Mar. 27, 2014_Non-Final_Offic Action.
- U.S. Appl. No. 14/099,562, filed Jul. 2, 2014_Final_Offic Action.
- U.S. Appl. No. 14/099,562, filed Dec. 10, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,571, filed Mar. 28, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,571, filed Jul. 15, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,582, filed Apr. 29, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,582, filed Jun. 17, 2014_Non-Final_Offic Action.
- U.S. Appl. No. 14/099,582, filed Nov. 7, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,582, filed Jan. 22, 2015_Notice_of_Allowance.
- U.S. Appl. No. 14/099,598, filed May 13, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,598, filed Jul. 3, 2014_Non-Final_Offic Action.
- U.S. Appl. No. 14/099,598, filed Dec. 10, 2014_Notice_of_Allowance.
- U.S. Appl. No. 14/099,612, filed Mar. 20, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,612, filed Oct. 30, 2014_Non-Final_Offic Action.
- U.S. Appl. No. 14/099,612, filed Nov. 26, 2014_Notice_of_Allowance.

US 10,675,288 B2

Page 18

(56)

References Cited

OTHER PUBLICATIONS

- U.S. Appl. No. 14/099,623, filed Mar. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,623, filed Jul. 18, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,623, filed Dec. 15, 2014_Note_of_Allowance.
- U.S. Appl. No. 14/106,655, filed Jul. 3, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/106,655, filed Dec. 8, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/106,655, filed Jun. 19, 2015 Final Office Action.
- U.S. Appl. No. 14/125,554, filed Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/125,554, filed Apr. 14, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/136,048, filed Nov. 4, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/136,048, filed Mar. 12, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,814, filed Oct. 1, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,814, filed Feb. 13, 2015_Note_of_Allowance.
- U.S. Appl. No. 14/475,864, filed Oct. 2, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,864, filed Feb. 11, 2015_Note_of_Allowance.
- U.S. Appl. No. 14/521,230, filed Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/521,230, filed Feb. 18, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/624,051, filed Apr. 7, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/690,955, filed Feb. 1, 2016_Non-Final_Office_Action.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens, *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.
- Voegtlne et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.
- Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.
- Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role for the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).
- Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforbes.es/1LIUm1V> on Feb. 23, 2015, 3 pages.
- Whitehead et al., Absorption and metabolism of oral progesterone, *The British Medical Journal*, vol. 280, No. 6217 (Mar. 22, 1980), pp. 825-827, BMJ Publishing Group.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Wood et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, *Breast Cancer Res Treat* (2007) 101:125-134.
- Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
- Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, *Handbook of Acqueous Solubility Data, Solutions*, 2003, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.
- Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid.
- Ettinger et al., "Measuring symptom relief in studies of vaginal and vulvar atrophy: the most bothersome symptom approach," *Menopause*, vol. 15, No. 5, 2008, pp. 885-889.
- Eugster-Hausmann et al., "Minimized estradiol absorption with ultra-low-dose 10 µg 17β-estradiol vaginal tablets," *Climacteric* 2010;13:219-227.
- Hitchcock, Christine L. et al., "Oral micronized progesterone for vasomotor symptoms—a placebo-controlled randomized trial in healthy postmenopausal women," *Menopause: The Journal of the North American Menopause Society*. 19(8):886-893, Aug. 2012.
- March, Charles M. et al., "Roles of Estradiol and Progesterone in Eliciting the Midcycle Luteinizing Hormone and Follicle-Stimulating Hormone Surges," *The Journal of Clinical Endocrinology & Metabolism*, vol. 49, Issue 4, Oct. 1, 1979, pp. 507-513.
- Simon, James A. et al., "A vaginal estradiol softgel capsule, TX-004HR, has negligible to verylow systemic absorption of estradiol: Efficacy and pharmacokineticdata review," *Maturitas* 99 (2017) 51-58.
- Sofi, Showkat Hussain et al., "Gelucire: A Versatile Formulation Excipient," *Ijppr.Human*, 2017; vol. 10 (3): 55-73.
- Stefanick, "Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration," *The American Journal of Medicine* (2005) vol. 118 (12B), 64S-73S.
- U.S. Appl. No. 16/104,101, filed Aug. 16, 2018.
- U.S. Appl. No. 16/125,201, filed Sep. 7, 2018.
- Hosmer, Jaclyn et al., "Microemulsions Containing Medium-Chain Glycerides as Transdermal Delivery Systems for Hydrophilic and Hydrophobic Drugs," *AAPS PharmSciTech*, 2009, vol. 10, No. 2, pp. 589-596.
- U.S. Appl. No. 13/684,002, filed Nov. 21, 2012, U.S. Pat. No. 8,633,178, Jan. 21, 2014.
- U.S. Appl. No. 13/843,362, filed Mar. 15, 2013.
- U.S. Appl. No. 13/843,428, filed Mar. 15, 2013, U.S. Pat. No. 9,301,920, Apr. 5, 2016.
- U.S. Appl. No. 14/099,545, filed Dec. 6, 2013, U.S. Pat. No. 8,846,648, Sep. 30, 2014.
- U.S. Appl. No. 14/099,562, filed Dec. 6, 2013, U.S. Pat. No. 8,987,237, Mar. 24, 2015.
- U.S. Appl. No. 14/099,571, filed Dec. 6, 2013, U.S. Pat. No. 8,846,649, Sep. 30, 2014.
- U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, U.S. Pat. No. 9,012,434, Apr. 21, 2015.
- U.S. Appl. No. 14/099,598, filed Dec. 6, 2013, U.S. Pat. No. 8,987,238, Mar. 24, 2015.
- U.S. Appl. No. 14/099,612, filed Dec. 6, 2013, U.S. Pat. No. 8,933,059, Jan. 13, 2015.
- U.S. Appl. No. 14/099,623, filed Dec. 6, 2013, U.S. Pat. No. 9,006,222, Apr. 14, 2015.
- U.S. Appl. No. 14/106,655, filed Dec. 13, 2013.

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Page 19

(56)

References Cited

OTHER PUBLICATIONS

U.S. Appl. No. 14/125,554, filed Jan. 25, 2013, U.S. Pat. No. 9,248,136, Feb. 2, 2016.
U.S. Appl. No. 14/136,048, filed Dec. 20, 2013, U.S. Pat. No. 9,180,091, Nov. 10, 2015.
U.S. Appl. No. 14/475,814, filed Sep. 3, 2014, U.S. Pat. No. 8,993,548, Mar. 31, 2015.
U.S. Appl. No. 14/475,864, filed Sep. 3, 2014, U.S. Pat. No. 8,993,549, Mar. 31, 2015.
U.S. Appl. No. 14/475,946, filed Sep. 3, 2014, U.S. Pat. No. 9,114,145, Aug. 25, 2015.
U.S. Appl. No. 14/476,040, filed Sep. 3, 2014, U.S. Pat. No. 9,114,146, Aug. 25, 2015.
U.S. Appl. No. 14/512,046, filed Oct. 10, 2014.
U.S. Appl. No. 14/521,002, filed Oct. 22, 2014.
U.S. Appl. No. 14/521,230, filed Oct. 22, 2014.
U.S. Appl. No. 14/624,051, filed Feb. 17, 2015, U.S. Pat. No. 9,289,382, Mar. 22, 2016.
U.S. Appl. No. 14/649,818, filed Jun. 18, 2013.

U.S. Appl. No. 14/690,913, filed Apr. 20, 2015.
U.S. Appl. No. 14/690,955, filed Apr. 20, 2015.
U.S. Appl. No. 14/719,933, filed May 22, 2015.
U.S. Appl. No. 14/812,179, filed Jul. 29, 2015.
U.S. Appl. No. 14/830,398, filed Aug. 19, 2015.
U.S. Appl. No. 15/372,385, filed Dec. 7, 2016.
U.S. Appl. No. 15/420,019, filed Jan. 30, 2017.
U.S. Appl. No. 15/475,052, filed Mar. 30, 2017.
U.S. Appl. No. 15/475,068, filed Mar. 30, 2017.
U.S. Appl. No. 15/781,840, filed Jun. 6, 2018.
U.S. Appl. No. 15/832,750, filed Dec. 5, 2017.
U.S. Appl. No. 15/832,757, filed Dec. 5, 2017.
U.S. Appl. No. 15/893,542, filed Feb. 9, 2018.
U.S. Appl. No. 15/893,546, filed Feb. 9, 2018.
U.S. Appl. No. 15/893,550, filed Feb. 9, 2018.
U.S. Appl. No. 15/975,723, filed May 9, 2018.
U.S. Appl. No. 15/975,733, filed May 9, 2018.
U.S. Appl. No. 16/004,338, filed Jun. 8, 2018.
U.S. Appl. No. 16/006,721, filed Jun. 12, 2018.

* cited by examiner

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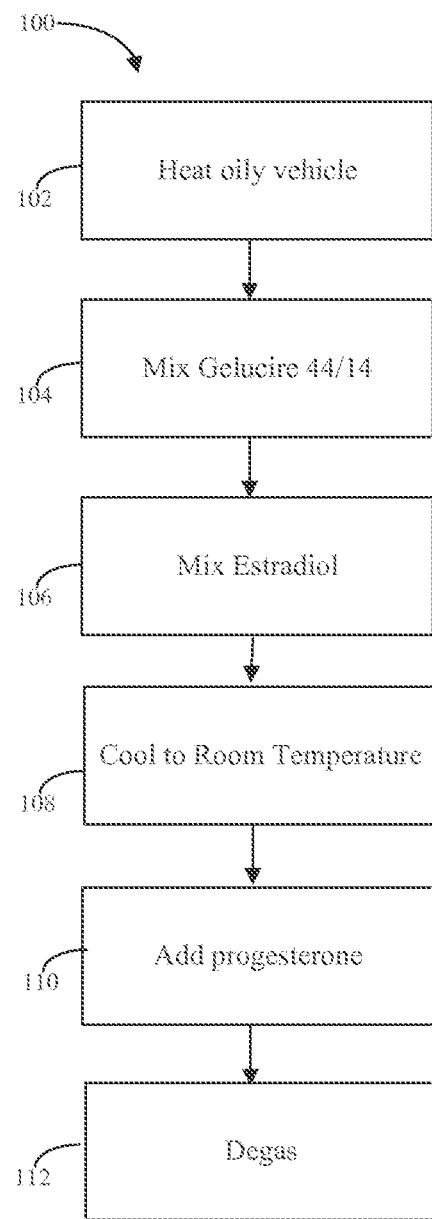


Fig. 1

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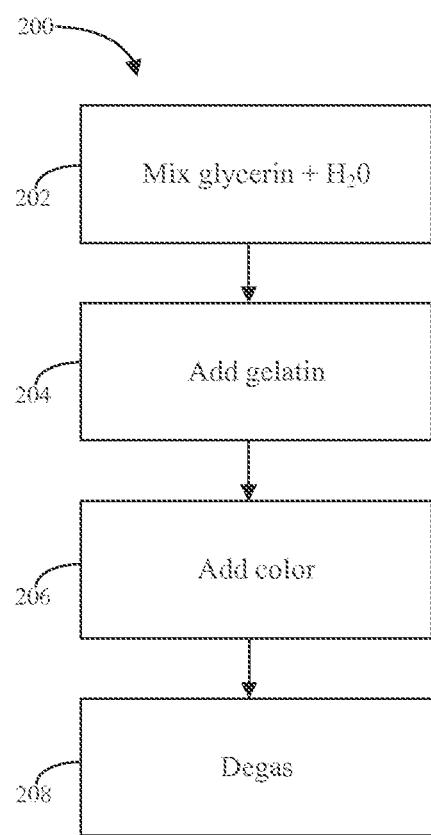


Fig. 2

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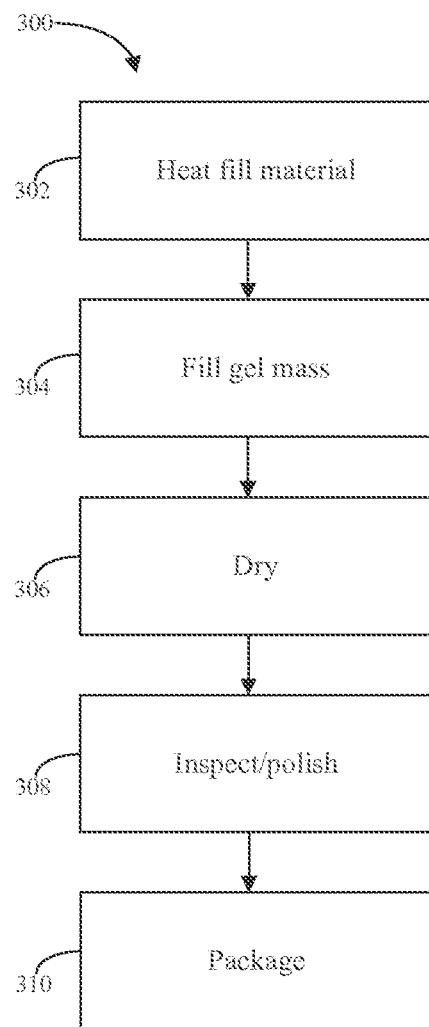


Fig. 3

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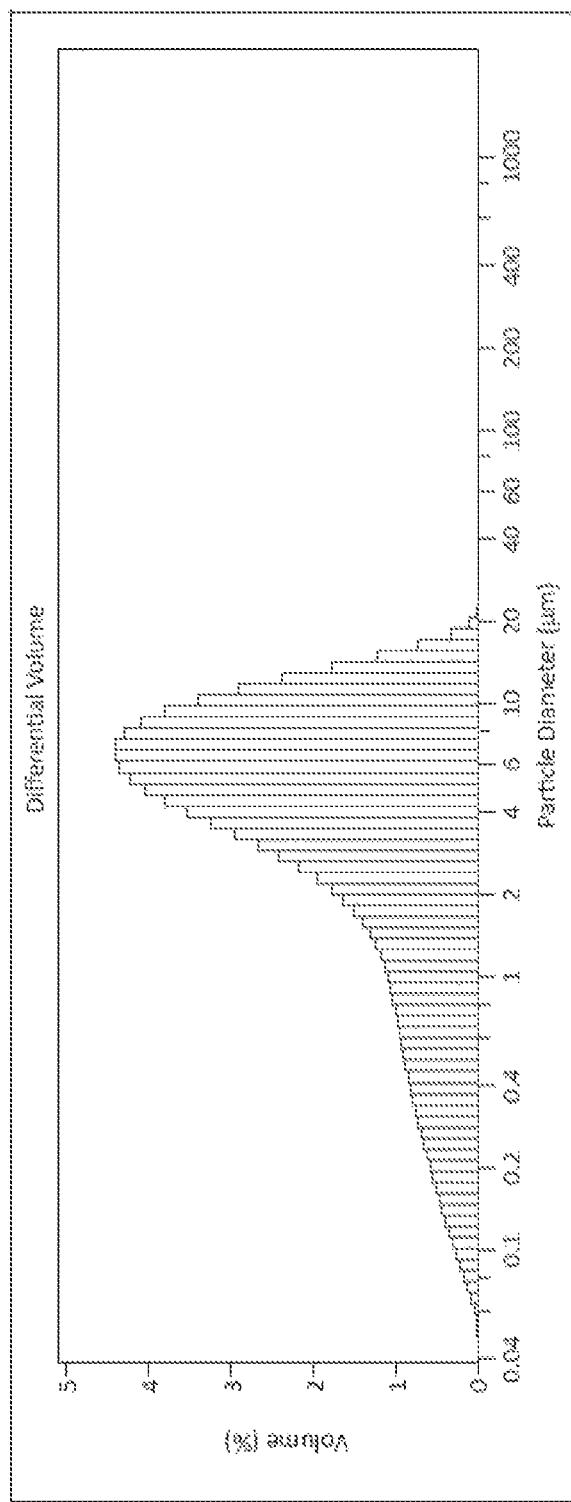


FIG. 4

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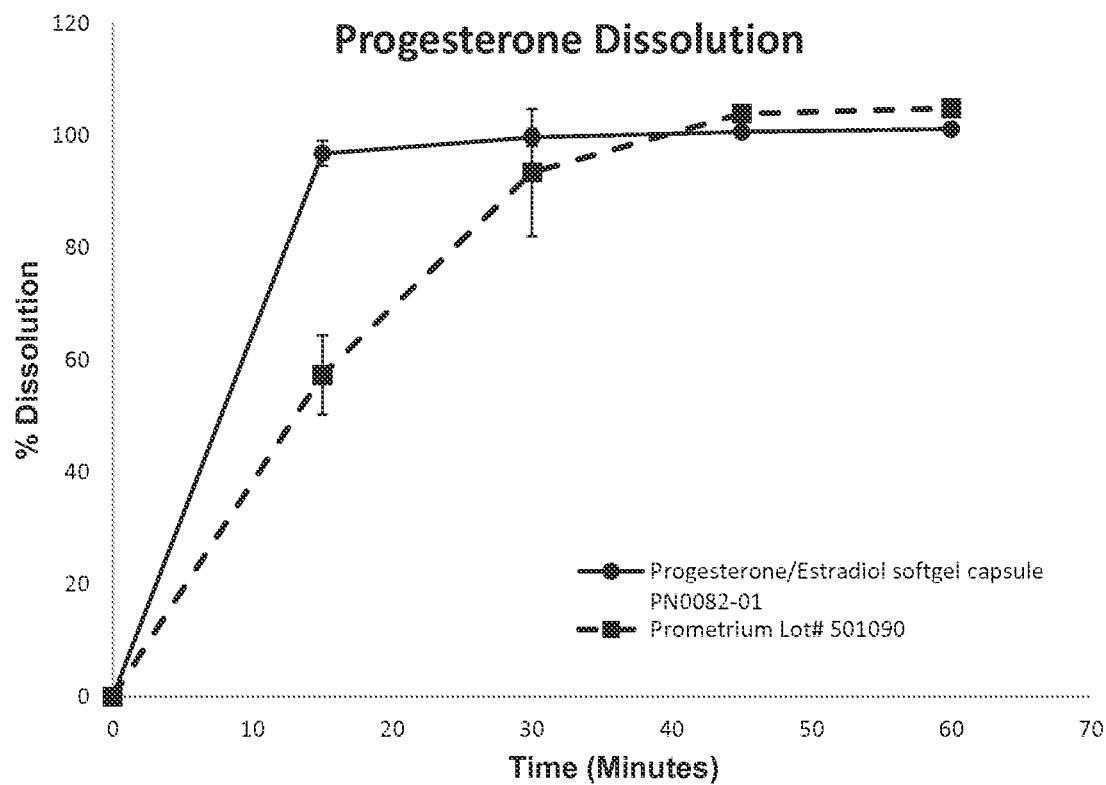


FIG. 5

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application claims priority to the following U.S. patent applications: U.S. application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013; U.S. application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES," which was filed on Nov. 21, 2012; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

BACKGROUND

Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

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Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

5 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

10 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

15 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA # N019781. According to the prescribing information approved for this product 20 (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

25 Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

**BRIEF DESCRIPTION OF THE
DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

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FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “Cmax” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

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The term, “Tmax” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, Cmax and, optionally, Tmax are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution, i.e., at least 98% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation

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may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Prometrium Capsules Daily Dose			
Parameter	100 mg	200 mg	300 mg
C _{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T _{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC ₀₋₁₀ (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

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Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

- 5 Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method 10 of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as 15 described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes 20 and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and 25 each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the 30 disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.
- 35 Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol 40 (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol 45 and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 50 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for 55 each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

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Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm . The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or trigly-

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erides and combinations and derivatives thereof a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and diglycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50 C, e.g., at or below 50 C, at or below 40 C, or at or below 50 C. In illustrative embodiments, Gelucire 44/14 is heated to about 65 C and Capmul MCM is heated to about 40 C to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments,

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the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monocaprylate, e.g., Capryol™ 90 (Gattefosse).

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In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20 C, are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and Labarafil® corn/apricot oil PEG-6 esters (Gattefosse).

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

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For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

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-continued

Formulation B- P: 50/EE: 0.5:		
	Ingredient(s)	Amount (% w/w)
		Qty/Capsule (mg)
5	Estradiol	0.35
	Hemihydrate	0.52
10	Capmul	65.32
	MCM, NF	97.98
	Gelucire	1.00
15	44/14, NF	1.50
	Total	100.00
		150.00

Formulation C - P: 100/EE: 0.5:		
	Ingredient(s)	Amount (% w/w)
		Qty/Capsule (mg)
20	Progesterone, USP, micronized	33.33
	Estradiol	0.17
25	Hemihydrate	0.52
	Capmul	65.49
30	MCM, NF	196.48
	Gelucire	1.00
35	44/14, NF	3.00
	Total	100.00
		300.00

Formulation D - P: 100/EE: 1:		
	Ingredient(s)	Amount (% w/w)
		Qty/Capsule (mg)
35	Progesterone, USP, micronized	33.33
	Estradiol	0.34
40	Hemihydrate	1.03
	Capmul	65.32
45	MCM, NF	195.97
	Gelucire	1.00
50	44/14, NF	3.00
	Total	100.00
		300.00

Formulation A- P: 50/EE: 0.25:		
	Ingredient(s)	Amount (% w/w)
		Qty/Capsule (mg)
	Progesterone, USP, micronized	33.33
	Estradiol	0.17
50	Hemihydrate	0.26
	Capmul	65.49
	MCM, NF	98.24
	Gelucire	1.00
55	44/14, NF	1.50
	Total	100.00
		150.00

Formulation B- P: 50/EE: 0.5:		
	Ingredient(s)	Amount (% w/w)
		Qty/Capsule (mg)
	Progesterone, USP, micronized	33.33
		50.00

Formulation E- P: 200/EE: 2:		
	Ingredient(s)	Amount (% w/w)
		Qty/Capsule (mg)
50	Progesterone, USP, micronized	33.33
	Estradiol	0.34
55	Hemihydrate	2.06
	Capmul	65.32
60	MCM, NF	391.94
	Gelucire	1.00
65	44/14, NF	6.00
	Total	100.00
		600.00

*Note: 1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol

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hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone

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acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in Miglyol:ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labrasol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60

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TABLE 2-continued

Ingredient	Solubility (mg/g)
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol:Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol

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recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	Clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

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Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

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Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

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Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
		Total:	100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65 C and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
		Total:	100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
	Total:	100.00	600.0 mg	6000.0	

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65 C and Capmul MCM is heated to 40 C+/-5 C to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40 C; the mixture is then passed through a colloid mill, e.g., three times.

Example 15

Study 352—Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

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Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

5 Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods 10 for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed 15 to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription 20 medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

25 After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water 30 under fed condition, at ambient temperature in each period 35 under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

40 In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 45 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin 50 in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

55 At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C.±20° C. in the bio-analytical facility until analysis.

60 Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters Cmax, AUC0-t & AUC0-∞ were calculated on data obtained from 24 subjects 65 for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

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Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC _{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
AUC _{0-∞}	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{max}, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below for progesterone.

TABLE 19

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC _{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
AUC _{0-∞}	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

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Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combi-

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nations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

Example 17

Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @ 50° C. for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C, oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

Example 18

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone

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to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A method of treating an estrogen-deficient state in a female subject in need of treatment, the method comprising administering to the subject a capsule containing an effective amount of a pharmaceutical formulation comprising:
0.17 to 0.35 wt % solubilized estradiol,
30 to 35 wt % progesterone, comprising suspended micronized progesterone and solubilized progesterone,
55 to 75 wt % of an oil, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides comprising esters of C6 to C12 fatty acids, and
0.5 to 10 wt % nonionic surfactant;
wherein the solubilized estradiol, the suspended micronized progesterone, and the solubilized progesterone are present in the oil.
2. The method of claim 1, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides comprising esters of C6 to C10 fatty acids.

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3. The method of claim 1, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides comprising esters of C8 to C12 fatty acids.

4. The method of claim 1, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides comprising esters of C8 to C10 fatty acids.

5. The method of claim 1, wherein at least 90% of the total estradiol is solubilized.

6. The method of claim 1, wherein the non-ionic surfactant is lauroyl polyoxyl-32-glycerides.

7. The method of claim 1 wherein the capsule is a gelatin capsule.

8. The method of claim 1, wherein the progesterone is released more rapidly from the pharmaceutical composition than progesterone in peanut oil.

9. The method of claim 1, wherein the estrogen-deficient state is selected from the group consisting of a vasomotor symptom of menopause, sleep disturbances, mood changes, vulvovaginal atrophy, and osteoporosis.

10. The method of claim 1, wherein the estrogen-deficient state is a vasomotor symptom of menopause.

11. The method of claim 1, wherein the vasomotor symptom of menopause is selected from the group consisting of hot flashes and night sweats.

12. The method of claim 1, wherein the female subject is a post-menopausal woman.

13. A method of treating a vasomotor symptom of menopause in a female subject in need of treatment, the method comprising administering to the subject a capsule containing an effective amount of a pharmaceutical formulation comprising:

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0.17 to 0.35 wt % solubilized estradiol, 30 to 35 wt % progesterone, comprising suspended micronized progesterone and solubilized progesterone, 55 to 75 wt % of an oil, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides comprising predominantly esters of C6 to C12 fatty acids, and

0.5 to 10 wt % nonionic surfactant; wherein the solubilized estradiol, the suspended micronized progesterone, and the solubilized progesterone are present in the oil.

14. The method of claim 13, wherein the vasomotor symptom of menopause is selected from the group consisting of hot flashes and night sweats.

15. The method of claim 13, wherein the mammal is a post-menopausal woman.

16. A method of treating vulvovaginal atrophy in a female subject in need of treatment, the method comprising administering to the subject a capsule containing an effective amount of a pharmaceutical formulation comprising:

0.17 to 0.35 wt % solubilized estradiol, 30 to 35 wt % progesterone, comprising suspended micronized progesterone and solubilized progesterone, 55 to 75 wt % of an oil, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides comprising predominantly esters of C6 to C12 fatty acids, and

0.5 to 10 wt % nonionic surfactant; wherein the solubilized estradiol, the suspended micronized progesterone, and the solubilized progesterone are present in the oil.

* * * * *

EXHIBIT O



US011033626B2

(12) **United States Patent**
Cacace et al.

(10) **Patent No.:** US 11,033,626 B2
(45) **Date of Patent:** *Jun. 15, 2021

(54) **PROGESTERONE FORMULATIONS HAVING A DESIRABLE PK PROFILE**

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This patent is subject to a terminal disclaimer.

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CPC *A61K 47/14* (2013.01); *A61K 9/4825* (2013.01); *A61K 9/4858* (2013.01); *A61K 31/57* (2013.01)

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(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

1,967,351 A	7/1934	Doisy
2,232,438 A	2/1941	Butenandt

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI1001367 A2	7/2012
CN	102258455 A	11/2011

(Continued)

OTHER PUBLICATIONS

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)

(Continued)

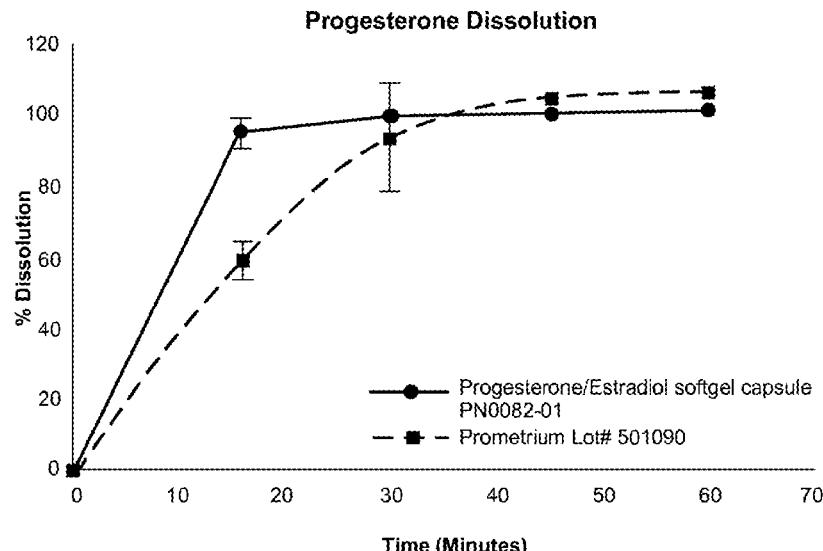
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(57) **ABSTRACT**

This disclosure provides progesterone formulations, methods of using these formulations, and their related pharmacokinetic parameters. In particular embodiments, the formulations disclosed herein allow for a reduction in the amount of progesterone administered to a patient in need thereof, while still providing the benefits of a larger dosage amount.

25 Claims, 10 Drawing Sheets



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Related U.S. Application Data

continuation of application No. 14/671,655, filed on Mar. 27, 2015, now abandoned, which is a continuation-in-part of application No. 14/125,547, filed as application No. PCT/US2013/046442 on Jun. 18, 2013, now Pat. No. 10,052,386, which is a continuation of application No. 13/843,362, filed on Mar. 15, 2013, and a continuation of application No. PCT/US2013/023309, filed on Jan. 25, 2013, and a continuation of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178, said application No. 14/671,655 is a continuation-in-part of application No. 13/843,428, filed on Mar. 15, 2013, now Pat. No. 9,301,920.

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(56) References Cited**U.S. PATENT DOCUMENTS**

2,379,832 A	7/1945	Serini et al.	4,629,449 A	12/1986	Wong
2,649,399 A	8/1953	Beall et al.	4,732,763 A	3/1988	Beck et al.
3,198,707 A	8/1965	Nomine et al.	4,738,957 A	4/1988	Laurent et al.
3,478,070 A	11/1969	Reinhardt et al.	4,756,907 A	7/1988	Beck et al.
3,526,648 A	9/1970	Daniel et al.	4,762,717 A	8/1988	Crowley, Jr.
3,710,795 A	1/1973	Higuchi et al.	4,788,062 A	11/1988	Gale et al.
3,729,560 A	4/1973	Hagerman	4,816,257 A	3/1989	Buster et al.
3,729,566 A	4/1973	Youngdale et al.	4,822,616 A	4/1989	Zimmermann et al.
3,755,573 A	8/1973	Berman	4,865,848 A	9/1989	Cheng et al.
3,755,575 A	8/1973	Lerner	4,900,734 A	2/1990	Maxson et al.
3,903,880 A	9/1975	Higuchi et al.	4,906,475 A	3/1990	Kim
3,916,898 A	11/1975	Robinson	4,942,158 A	7/1990	Sarpotdar et al.
3,916,899 A	11/1975	Theeuwes et al.	4,961,931 A	10/1990	Wong
3,921,636 A	11/1975	Zaffaroni	5,030,629 A	7/1991	Rajadhyaksha
3,923,997 A	12/1975	Meuly	5,064,654 A	11/1991	Berner et al.
3,948,254 A	4/1976	Zaffaroni	5,108,995 A	4/1992	Casper
3,971,367 A	7/1976	Zaffaroni	5,128,138 A	7/1992	Blank
3,977,404 A	8/1976	Theeuwes	5,130,137 A	7/1992	Crowley, Jr.
3,993,072 A	11/1976	Zaffaroni	5,140,021 A	8/1992	Maxson et al.
4,008,719 A	2/1977	Theeuwes et al.	5,211,952 A	5/1993	Spicer et al.
4,012,496 A	3/1977	Schopflin et al.	5,252,334 A	10/1993	Chiang et al.
4,014,334 A	3/1977	Theeuwes et al.	5,280,023 A	1/1994	Ehrlich et al.
4,014,987 A	3/1977	Heller et al.	5,288,496 A	2/1994	Lewis
4,016,251 A	4/1977	Higuchi et al.	5,340,584 A	8/1994	Spicer et al.
4,071,623 A	1/1978	Van Der Vies	5,340,585 A	8/1994	Pike et al.
4,093,709 A	6/1978	Choi et al.	5,340,586 A	8/1994	Pike et al.
4,154,820 A	5/1979	Simoons	5,362,497 A	11/1994	Yamada et al.
4,155,991 A	5/1979	Hartmann et al.	5,382,573 A	1/1995	Casper
4,196,188 A	4/1980	Besins	5,393,528 A	2/1995	Staab
4,215,691 A	8/1980	Wong	5,393,529 A	2/1995	Hoffmann et al.
4,237,885 A	12/1980	Pharriss et al.	5,419,910 A	5/1995	Lewis
4,310,510 A	1/1982	Sherman et al.	5,468,736 A	11/1995	Hodgen
4,327,725 A	5/1982	Cortese et al.	5,474,783 A	12/1995	Miranda et al.
4,372,951 A	2/1983	Vorys	5,480,776 A	1/1996	Dullien
4,384,096 A	5/1983	Sonnabend	5,514,673 A	5/1996	Heckenmueller et al.
4,393,871 A	7/1983	Vorhauer et al.	5,516,528 A	5/1996	Hughes et al.
4,402,695 A	9/1983	Wong	5,527,534 A	6/1996	Myhling
4,423,151 A	12/1983	Baranczuk	5,529,782 A	6/1996	Staab
4,449,980 A	5/1984	Millar et al.	5,538,736 A	7/1996	Hoffmann et al.
4,610,687 A	9/1986	Fogwell	5,543,150 A	8/1996	Bologna et al.
			5,547,948 A	8/1996	Barcomb
			5,556,635 A	9/1996	Istin et al.
			5,565,199 A	10/1996	Page et al.
			5,567,831 A	10/1996	Li
			5,569,652 A	10/1996	Beier et al.
			5,580,572 A	12/1996	Mikler et al.
			5,582,592 A	12/1996	Kendrick
			5,585,370 A	12/1996	Casper
			5,595,759 A	1/1997	Wright et al.
			5,595,970 A	1/1997	Garfield et al.
			5,605,702 A	2/1997	Teillaud et al.
			5,607,691 A	3/1997	Hale et al.
			5,607,693 A	3/1997	Bonte et al.
			5,609,617 A	3/1997	Shealy et al.
			5,620,705 A	4/1997	Dong et al.
			5,626,866 A	5/1997	Ebert et al.
			5,629,021 A	5/1997	Wright
			5,633,011 A	5/1997	Dong et al.
			5,633,242 A	5/1997	Oettel et al.
			5,639,743 A	6/1997	Kaswan et al.
			5,653,983 A	8/1997	Meybeck et al.
			5,656,286 A	8/1997	Miranda et al.
			5,660,839 A	8/1997	Allee et al.
			5,662,927 A	9/1997	Ehrlich et al.
			5,663,160 A	9/1997	Meybeck et al.
			5,676,968 A	10/1997	Lipp et al.
			5,677,292 A	10/1997	Li et al.
			5,686,097 A	11/1997	Taskovich et al.
			5,693,335 A	12/1997	Xia et al.
			5,694,947 A	12/1997	Lehtinen et al.
			5,700,480 A	12/1997	Hille et al.
			5,709,844 A	1/1998	Arbeit et al.
			5,719,197 A	2/1998	Kanios et al.
			5,735,801 A	4/1998	Caillouette
			5,739,176 A	4/1998	Dunn et al.
			5,744,463 A	4/1998	Bair
			5,747,058 A	5/1998	Tipton et al.
			5,762,614 A	6/1998	Caillouette
			5,770,176 A	6/1998	Nargessi

US 11,033,626 B2

Page 3

(56)	References Cited				
U.S. PATENT DOCUMENTS					
5,770,219 A	6/1998	Chiang et al.	6,139,873 A	10/2000	Hughes, Jr. et al.
5,770,220 A	6/1998	Meconi et al.	6,149,935 A	11/2000	Chiang et al.
5,770,227 A	6/1998	Dong et al.	6,153,216 A	11/2000	Cordes et al.
5,776,495 A	7/1998	Duclos et al.	6,165,491 A	12/2000	Grasset et al.
5,780,044 A	7/1998	Yewey et al.	6,165,975 A	12/2000	Adams et al.
5,780,050 A	7/1998	Jain et al.	6,187,323 B1	2/2001	Aiache et al.
5,788,980 A	8/1998	Nabahi	6,187,339 B1	2/2001	De Haan et al.
5,788,984 A	8/1998	Guenther et al.	6,190,331 B1	2/2001	Caillouette
5,789,442 A	8/1998	Garfield et al.	6,201,072 B1	3/2001	Rathi et al.
5,811,416 A	9/1998	Chwalisz et al.	6,217,886 B1	4/2001	Önyüksel et al.
5,811,547 A	9/1998	Nakamichi et al.	6,225,297 B1	5/2001	Stockemann et al.
5,814,329 A	9/1998	Shah	6,227,202 B1	5/2001	Matapurkar
5,820,878 A	10/1998	Hirano et al.	6,228,383 B1	5/2001	Hansen et al.
5,827,200 A	10/1998	Caillouette	6,228,852 B1	5/2001	Shaak
5,840,327 A	11/1998	Gale et al.	6,242,509 B1	6/2001	Berger et al.
5,843,468 A	12/1998	Burkoth et al.	6,245,811 B1	6/2001	Horrobin et al.
5,843,979 A	12/1998	Wille et al.	6,262,115 B1	7/2001	Guittard et al.
5,858,394 A	1/1999	Lipp et al.	6,264,980 B1	7/2001	Hille
5,863,552 A	1/1999	Yue	6,267,984 B1	7/2001	Beste et al.
5,866,603 A	2/1999	Li et al.	6,274,165 B1	8/2001	Meconi et al.
5,882,676 A	3/1999	Lee et al.	6,277,418 B1	8/2001	Markaverich et al.
5,885,612 A	3/1999	Meconi et al.	6,283,927 B1	9/2001	Caillouette
5,888,533 A	3/1999	Dunn	6,287,588 B1	9/2001	Shih et al.
5,891,462 A	4/1999	Carrara	6,287,693 B1	9/2001	Savoir et al.
5,891,868 A	4/1999	Cummings et al.	6,294,188 B1	9/2001	Ragavan et al.
5,898,038 A	4/1999	Yallampalli et al.	6,294,192 B1	9/2001	Patel et al.
5,902,603 A	5/1999	Chen et al.	6,294,550 B1	9/2001	Place et al.
5,904,931 A	5/1999	Lipp et al.	6,299,900 B1	10/2001	Reed et al.
5,906,830 A	5/1999	Farinas et al.	6,303,132 B1	10/2001	Nelson
5,912,010 A	6/1999	Wille et al.	6,303,588 B1	10/2001	Danielov
5,916,176 A	6/1999	Caillouette	6,306,841 B1	10/2001	Place et al.
RE36,247 E	7/1999	Plunkett et al.	6,306,914 B1	10/2001	De Ziegler et al.
5,919,477 A	7/1999	Bevan et al.	6,309,669 B1	10/2001	Setterstrom et al.
5,922,349 A	7/1999	Elliesen et al.	6,309,848 B1	10/2001	Howett et al.
5,928,666 A	7/1999	Farinas et al.	6,312,703 B1	11/2001	Orthofer
5,942,243 A	8/1999	Shah	6,328,987 B1	12/2001	Marini
5,952,000 A	9/1999	Venkateshwaran et al.	6,342,491 B1	1/2002	Dey et al.
5,958,446 A	9/1999	Miranda et al.	6,344,211 B1	2/2002	Hille
5,962,445 A	10/1999	Stewart	6,372,209 B1	4/2002	Chrisope
5,968,919 A	10/1999	Samour et al.	6,372,245 B1	4/2002	Bowman et al.
5,972,372 A	10/1999	Saleh et al.	6,372,246 B1	4/2002	Wei et al.
5,985,311 A	11/1999	Cordes et al.	6,387,390 B1	5/2002	Deaver et al.
5,985,850 A	11/1999	Falk et al.	6,402,705 B1	6/2002	Caillouette
5,985,861 A	11/1999	Levine et al.	6,416,778 B1	7/2002	Ragavan et al.
5,989,568 A	11/1999	Breton et al.	6,420,352 B1	7/2002	Knowles
5,993,856 A	11/1999	Ragavan et al.	6,423,039 B1	7/2002	Rathbone et al.
6,001,846 A	12/1999	Edwards et al.	6,423,683 B1	7/2002	Heaton et al.
6,007,835 A	12/1999	Bon-Lapillonne et al.	6,432,438 B1	8/2002	Shukla
6,010,715 A	1/2000	Wick et al.	6,436,633 B1	8/2002	Kreider et al.
6,013,276 A	1/2000	Math et al.	6,440,454 B1	8/2002	Santoro et al.
6,022,562 A	2/2000	Autant et al.	6,444,224 B1	9/2002	Rathbone et al.
6,024,974 A	2/2000	Li	6,444,234 B1	9/2002	Kirby et al.
6,024,976 A	2/2000	Miranda et al.	6,451,300 B1	9/2002	Dunlop et al.
6,028,057 A	2/2000	Burns	6,451,339 B2	9/2002	Patel et al.
6,030,948 A	2/2000	Mann	6,451,779 B1	9/2002	Hesch
6,039,968 A	3/2000	Nabahi	6,455,246 B1	9/2002	Howett et al.
6,040,340 A	3/2000	Chwalisz et al.	6,455,517 B1	9/2002	Tanabe et al.
6,056,972 A	5/2000	Hermsmeyer	6,469,016 B1	10/2002	Rossi-Montero et al.
6,060,077 A	5/2000	Meignant	6,472,434 B1	10/2002	Place et al.
6,068,853 A	5/2000	Giannos et al.	6,479,232 B1	11/2002	Howett et al.
6,074,625 A	6/2000	Hawthorne et al.	6,495,160 B2	12/2002	Esposito et al.
6,077,531 A	6/2000	Salin-Drouin	6,500,814 B1	12/2002	Hesch
6,080,118 A	6/2000	Blythe	6,503,896 B1	1/2003	Tanabe et al.
6,083,178 A	7/2000	Caillouette	6,511,969 B1	1/2003	Hermsmeyer
6,086,916 A	7/2000	Agnus et al.	6,521,250 B2	2/2003	Meconi et al.
6,087,352 A	7/2000	Trout	6,526,980 B1	3/2003	Tracy et al.
6,090,404 A	7/2000	Meconi et al.	6,528,094 B1	3/2003	Savoir et al.
6,096,338 A	8/2000	Lacy et al.	6,531,149 B1	3/2003	Kirstgen et al.
6,106,848 A	8/2000	Preuilh et al.	6,537,580 B1	3/2003	Savoir et al.
6,117,446 A	9/2000	Place	6,538,039 B2	3/2003	Laurent
6,117,450 A	9/2000	Dittgen et al.	6,544,196 B2	4/2003	Caillouette
6,124,362 A	9/2000	Bradbury et al.	6,544,553 B1	4/2003	Hsia et al.
6,133,251 A	10/2000	Dittgen et al.	6,548,053 B1	4/2003	Stewart et al.
6,133,320 A	10/2000	Yallampalli et al.	6,548,491 B2	4/2003	Tanabe et al.
6,139,868 A	10/2000	Hoffmann	6,551,611 B2	4/2003	Elliesen et al.

US 11,033,626 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,555,131 B1	4/2003	Wolff et al.	7,094,228	B2	8/2006	Zhang et al.
6,562,367 B1	5/2003	Wolff et al.	7,097,853	B1	8/2006	Garbe et al.
6,562,370 B2	5/2003	Luo et al.	7,101,342	B1	9/2006	Caillouette
6,562,790 B2	5/2003	Chein et al.	7,105,573	B2	9/2006	Krajcik et al.
6,569,463 B2	5/2003	Patel et al.	7,135,190	B2	11/2006	Piao et al.
6,583,129 B1	6/2003	Mazer et al.	7,153,522	B1	12/2006	Ikeura et al.
6,586,006 B2	7/2003	Roser et al.	7,163,681	B2	1/2007	Giles-Komar et al.
6,589,549 B2	7/2003	Shih et al.	7,163,699	B2	1/2007	Besse
6,593,317 B1	7/2003	De Ziegler et al.	7,175,850	B2	2/2007	Cevc
6,599,519 B1	7/2003	Seo et al.	7,179,799	B2	2/2007	Hill et al.
6,610,652 B2	8/2003	Heaton et al.	7,196,074	B2	3/2007	Blye et al.
6,610,670 B2	8/2003	Backensfeld et al.	7,198,800	B1	4/2007	Ko
6,610,674 B1	8/2003	Schreiber	7,198,801	B2	4/2007	Carrara et al.
6,635,274 B1	10/2003	Masiz et al.	7,226,910	B2	6/2007	Wilson et al.
6,638,528 B1	10/2003	Kanios	7,247,625	B2	7/2007	Zhang et al.
6,638,536 B2	10/2003	Savoir et al.	7,250,446	B2	7/2007	Council
6,645,528 B1	11/2003	Straub et al.	7,267,829	B2	9/2007	Kirby et al.
6,649,155 B1	11/2003	Dunlop et al.	7,300,926	B2	11/2007	Prokai et al.
6,653,298 B2	11/2003	Potter et al.	7,303,763	B2	12/2007	Ho
6,656,929 B1	12/2003	Agnus et al.	7,317,037	B2	1/2008	Fensome et al.
6,660,726 B2	12/2003	Hill et al.	7,329,654	B2	2/2008	Kanojia et al.
6,663,608 B2	12/2003	Rathbone et al.	7,335,650	B2	2/2008	Potter et al.
6,663,895 B2	12/2003	Savoir et al.	7,374,779	B2	5/2008	Chen et al.
6,682,757 B1	1/2004	Wright	7,378,404	B2	5/2008	Peters et al.
6,692,763 B1	2/2004	Cummings et al.	7,381,427	B2	6/2008	Ancira et al.
6,708,822 B1	3/2004	Muni	7,387,789	B2	6/2008	Klose et al.
6,720,001 B2	4/2004	Chen et al.	7,388,006	B2	6/2008	Schmees et al.
6,737,081 B2	5/2004	Savoir et al.	7,414,043	B2	8/2008	Kosemund et al.
6,740,333 B2	5/2004	Beckett et al.	7,427,413	B2	9/2008	Savoir et al.
6,743,448 B2	6/2004	Kryger	7,427,609	B2	9/2008	Leonard
6,743,815 B2	6/2004	Huebner et al.	7,429,576	B2	9/2008	Labrie
6,747,018 B2	6/2004	Tanabe et al.	7,431,941	B2	10/2008	Besins et al.
6,750,291 B2	6/2004	Kim et al.	7,456,159	B2	11/2008	Houze et al.
6,756,208 B2	6/2004	Griffin et al.	7,459,445	B2	12/2008	Hill et al.
6,776,164 B2	8/2004	Bunt et al.	7,465,587	B2	12/2008	Imrich et al.
6,787,152 B2	9/2004	Kirby et al.	7,470,433	B2	12/2008	Carrara et al.
6,805,877 B2	10/2004	Massara et al.	7,485,666	B2	2/2009	Villanueva et al.
6,809,085 B1	10/2004	Elson et al.	7,497,855	B2	3/2009	Ausiello et al.
6,818,226 B2	11/2004	Reed et al.	7,498,303	B2	3/2009	Arnold et al.
6,821,524 B2	11/2004	Marini	7,534,765	B2	5/2009	Gregg et al.
6,841,716 B1	1/2005	Tsutsumi	7,534,780	B2	5/2009	Wyrwa et al.
6,844,334 B2	1/2005	Hill et al.	7,550,142	B2	6/2009	Giles-Komar et al.
6,855,703 B1	2/2005	Hill et al.	7,563,565	B1	7/2009	Matsuo et al.
6,860,859 B2	3/2005	Mehrotra et al.	7,569,274	B2	8/2009	Besse et al.
6,866,865 B2	3/2005	Hsia et al.	7,572,779	B2	8/2009	Aloba et al.
6,869,969 B2	3/2005	Huebner et al.	7,572,780	B2	8/2009	Hermsmeyer
6,878,518 B2	4/2005	Whitehead	7,589,082	B2	9/2009	Savoir et al.
6,901,278 B1	5/2005	Notelovitz	7,671,027	B2	3/2010	Loumaye
6,905,705 B2	6/2005	Palm et al.	7,674,783	B2	3/2010	Hermsmeyer
6,911,211 B2	6/2005	Eini et al.	7,687,281	B2	3/2010	Roth et al.
6,911,438 B2	6/2005	Wright	7,687,485	B2	3/2010	Levinson et al.
6,923,988 B2	8/2005	Patel et al.	7,694,683	B2	4/2010	Callister et al.
6,924,274 B2	8/2005	Lardy et al.	7,704,983	B1	4/2010	Hodgen et al.
6,932,983 B1	8/2005	Straub et al.	7,727,720	B2	6/2010	Dhallan
6,939,558 B2	9/2005	Massara et al.	7,732,408	B2	6/2010	Josephson et al.
6,943,021 B2	9/2005	Klausner et al.	7,749,989	B2	7/2010	Hill et al.
6,958,327 B1	10/2005	Hillisch et al.	7,767,656	B2	8/2010	Shoichet et al.
6,960,337 B2	11/2005	Daniels et al.	7,799,769	B2	9/2010	White et al.
6,962,691 B1	11/2005	Lulla et al.	7,815,936	B2	10/2010	Hasenzahl et al.
6,962,908 B2	11/2005	Aloba et al.	7,815,949	B2	10/2010	Cohen
6,967,194 B1	11/2005	Matsuo et al.	7,829,115	B2	11/2010	Besins et al.
6,974,569 B2	12/2005	Dunlop et al.	7,829,116	B2	11/2010	Griswold et al.
6,977,250 B2	12/2005	Rodriguez	RE42,012	E	12/2010	Deaver et al.
6,978,945 B2	12/2005	Wong et al.	7,850,992	B2	12/2010	Kim et al.
6,995,149 B1	2/2006	Endrikat et al.	7,854,753	B2	12/2010	Kraft et al.
7,004,321 B1	2/2006	Palm et al.	7,858,607	B2	12/2010	Manchur
7,005,429 B2	2/2006	Dey et al.	RE42,072	E	1/2011	Deaver et al.
7,011,846 B2	3/2006	Shojaei et al.	7,862,552	B2	1/2011	McIntyre et al.
7,018,992 B2	3/2006	Koch et al.	7,867,990	B2	1/2011	Schultz et al.
7,030,104 B2	4/2006	Gray et al.	7,871,643	B2	1/2011	Lizio et al.
7,030,157 B2	4/2006	Ke et al.	7,879,830	B2	2/2011	Wiley
RE39,104 E	5/2006	Duclos et al.	7,884,093	B2	2/2011	Creasy et al.
7,074,779 B2	7/2006	Sui et al.	7,925,519	B2	4/2011	Greene
7,083,590 B1	8/2006	Bunt et al.	7,939,104	B2	5/2011	Barbera et al.
7,091,213 B2	8/2006	Metcalf et al.	7,943,602	B2	5/2011	Bunschoten et al.
			7,943,604	B2	5/2011	Coelingh et al.
			7,945,459	B2	5/2011	Grace et al.
			7,960,368	B2	6/2011	Nickisch et al.
			7,989,436	B2	8/2011	Hill et al.

US 11,033,626 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
7,989,487 B2	8/2011	Welsh et al.	8,486,374 B2	7/2013	Tamarkin et al.	
8,022,053 B2	9/2011	Mueller et al.	8,486,442 B2	7/2013	Matsushita et al.	
8,048,017 B2	11/2011	Xu	8,492,368 B2	7/2013	Vanlandingham et al.	
8,048,869 B2	11/2011	Bunschoten et al.	8,507,467 B2	8/2013	Matsui et al.	
8,063,030 B2	11/2011	Ellman	8,512,693 B2	8/2013	Capito et al.	
8,071,576 B2	12/2011	Coelingh et al.	8,512,754 B2	8/2013	Needham	
8,071,729 B2	12/2011	Giles-Komar et al.	8,536,159 B2	8/2013	Tamarkin et al.	
8,075,916 B2	12/2011	Song et al.	8,551,462 B2	9/2013	Li et al.	
8,075,917 B2	12/2011	Chung et al.	8,557,281 B2	9/2013	Barrett et al.	
8,076,317 B2	12/2011	Kulmann	8,568,374 B2	10/2013	Johnsson et al.	
8,076,319 B2	12/2011	Leonard	8,591,951 B2	10/2013	Goldstein et al.	
8,080,553 B2	12/2011	Keith et al.	8,613,951 B2	11/2013	Halliday et al.	
8,088,605 B2	1/2012	Beaudet et al.	8,633,178 B2 *	12/2013	De Graaff et al.	
8,096,940 B2	1/2012	Josephson et al.	1/2014	1/2014	Zale et al.	A61K 9/4858
8,101,209 B2	1/2012	Legrand et al.	8,633,180 B2	1/2014	Bernick A61K 9/4858	514/169
8,101,773 B2	1/2012	Smith et al.	8,636,787 B2	1/2014	Li et al.	
8,114,152 B2	2/2012	Furst	8,636,982 B2	1/2014	Sabaria	
8,114,434 B2	2/2012	Sasaki et al.	8,653,129 B2	2/2014	Tamarkin et al.	
8,114,442 B2	2/2012	Tucker et al.	8,658,627 B2	2/2014	Fein et al.	
8,119,741 B2	2/2012	Pavlin	8,658,628 B2	2/2014	Voskuhl	
8,121,886 B2	2/2012	Azar	8,663,681 B2	2/2014	Baucom	
8,124,118 B2	2/2012	Lennernas et al.	8,663,692 B1	3/2014	Ahmed et al.	
8,124,595 B2	2/2012	Boissonneault	8,663,703 B2	3/2014	Mueller et al.	
8,147,561 B2	4/2012	Bimmoeller	8,664,207 B2	3/2014	Lerner et al.	
8,148,546 B2	4/2012	Schuster et al.	8,669,293 B2	3/2014	Li et al.	
8,158,613 B2	4/2012	Stanforth et al.	8,679,552 B2	3/2014	Levy et al.	
8,158,614 B2	4/2012	Lambert et al.	8,694,358 B2	3/2014	Guthery	
8,163,722 B2	4/2012	Savoir et al.	8,697,127 B2	4/2014	Tryfon	
8,177,449 B2	5/2012	Bayly et al.	8,697,710 B2	4/2014	Sah	
8,182,833 B2	5/2012	Hermsmeyer	8,703,105 B2	4/2014	Li et al.	
8,187,615 B2	5/2012	Friedman	8,709,385 B2	4/2014	Tamarkin et al.	
8,195,403 B2	6/2012	Ishikawa et al.	8,709,451 B2	4/2014	Tamarkin et al.	
8,202,736 B2	6/2012	Mousa et al.	8,715,735 B2	4/2014	Rapoport et al.	
8,217,024 B2	7/2012	Ahmed et al.	8,721,331 B2	5/2014	Funke et al.	
8,221,785 B2	7/2012	Chien	8,722,021 B2	5/2014	Raghuprasad	
8,222,008 B2	7/2012	Theone et al.	8,734,846 B2	5/2014	Friedman et al.	
8,222,237 B2	7/2012	Nickisch et al.	8,735,381 B2	5/2014	Ali et al.	
8,227,454 B2	7/2012	Hill et al.	8,741,336 B2	6/2014	Mattern	
8,227,509 B2	7/2012	Castro et al.	8,741,373 B2	6/2014	Dipierro et al.	
8,241,664 B2	8/2012	Dudley et al.	8,753,661 B2	6/2014	Bromley et al.	
8,247,393 B2	8/2012	Ahmed et al.	8,784,882 B2	6/2014	Steinmuller-Nethl et al.	
8,257,724 B2	9/2012	Cromack et al.	8,815,261 B2	6/2014	Podolski	
8,257,725 B2	9/2012	Cromack et al.	8,846,648 B2 *	6/2014	Tryfon	
8,268,352 B2	9/2012	Vaya et al.	8,846,649 B2 *	9/2014	Sah	A61K 9/486
8,268,806 B2	9/2012	Labrie	8,846,649 B2 *	9/2014	Bernick A61K 9/486	514/169
8,268,878 B2	9/2012	Armer et al.	8,933,059 B2 *	9/2014	514/169	
8,273,730 B2	9/2012	Fernandez et al.	8,987,237 B2 *	9/2014	Bernick A61K 9/4825	
8,287,888 B2	10/2012	Song et al.	8,987,238 B2 *	9/2014	514/169	
8,288,366 B2	10/2012	Chochinov et al.	8,993,548 B2	9/2014	Bernick A61K 9/486	
8,318,898 B2	11/2012	Fasel et al.	8,993,549 B2	9/2014	514/169	
8,324,193 B2	12/2012	Lee-Sepsick et al.	9,006,222 B2 *	9/2014	Bernick A61K 9/7023	
8,329,680 B2	12/2012	Evans et al.	9,006,222 B2 *	9/2014	514/169	
8,337,814 B2	12/2012	Osbakken et al.	9,012,434 B2 *	9/2014	Bernick A61K 31/57	
8,344,007 B2	1/2013	Tang et al.	9,012,434 B2 *	9/2014	514/169	
8,349,820 B2	1/2013	Zeun et al.	9,114,145 B2 *	9/2014	Bernick A61K 47/10	
8,353,863 B2	1/2013	Imran	9,114,146 B2 *	9/2014	514/169	
8,357,723 B2	1/2013	Satyam	9,248,136 B2 *	9/2014	Bernick A61K 9/4825	
8,361,995 B2	1/2013	Schramm	9,301,920 B2 *	9/2014	514/169	
8,362,091 B2	1/2013	Tamarkin et al.	10,052,386 B2 *	9/2014	Bernick A61K 9/16	
8,372,424 B2	2/2013	Berry et al.	10,471,148 B2 *	9/2014	Bernick A61K 31/565	
8,372,806 B2	2/2013	Bohler et al.	10,639,375 B2 *	9/2014	6/2001	
8,377,482 B2	2/2013	Laurie et al.	2001/0005728 A1	6/2001	Bernick A61K 9/48	
8,377,994 B2	2/2013	Gray et al.	2001/0009673 A1	7/2001	Guittard et al.	
8,394,759 B2	3/2013	Barathur et al.	2001/0021816 A1	9/2001	Lipp et al.	
8,415,332 B2	4/2013	Diliberti et al.	2001/0023261 A1	9/2001	Cacace et al.	
8,420,111 B2	4/2013	Hermsmeyer	2001/0027189 A1	9/2001	Bennink et al.	
8,435,561 B2	5/2013	Besins et al.	2001/0029357 A1	10/2001	Bunt et al.	
8,435,972 B2	5/2013	Stein et al.	2001/0031747 A1	10/2001	Deziegler et al.	
8,449,879 B2	5/2013	Laurent-Applegate et al.	2001/0032125 A1	10/2001	Bhan et al.	
8,450,108 B2	5/2013	Boyce	2001/0034340 A1	10/2001	Pickar	
8,454,945 B2	6/2013	McCook et al.	2001/0053383 A1	10/2001	Miranda et al.	
8,455,468 B2	6/2013	Hoffman et al.				
8,461,138 B2	6/2013	Boissonneault				
8,476,252 B2	7/2013	Achleitner et al.				
8,481,488 B2	7/2013	Carter				

US 11,033,626 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2001/0056068 A1	12/2001	Chwalisz et al.	2004/0022820 A1	2/2004	Anderson	
2002/0012710 A1	1/2002	Lansky	2004/0034001 A1	2/2004	Karara	
2002/0026158 A1	2/2002	Rathbone et al.	2004/0037881 A1	2/2004	Guittard et al.	
2002/0028788 A1	3/2002	Bunt et al.	2004/0039356 A1	2/2004	Maki et al.	
2002/0035070 A1	3/2002	Gardlik et al.	2004/0043043 A1	3/2004	Schlyter et al.	
2002/0058648 A1	5/2002	Hammerly	2004/0043943 A1	3/2004	Guittard et al.	
2002/0058926 A1	5/2002	Rathbone et al.	2004/0044080 A1	3/2004	Place et al.	
2002/0064541 A1	5/2002	Lapidot et al.	2004/0048900 A1	3/2004	Flood	
2002/0076441 A1	6/2002	Shih et al.	2004/0052824 A1	3/2004	Abou et al.	
2002/0102308 A1	8/2002	Wei et al.	2004/0073024 A1	4/2004	Metcalf et al.	
2002/0107230 A1	8/2002	Waldon et al.	2004/0077605 A1	4/2004	Salvati et al.	
2002/0114803 A1	8/2002	Deaver et al.	2004/0077606 A1	4/2004	Salvati et al.	
2002/0119174 A1	8/2002	Gardlik et al.	2004/0087548 A1	5/2004	Salvati et al.	
2002/0119198 A1	8/2002	Gao et al.	2004/0087564 A1	5/2004	Wright et al.	
2002/0132801 A1	9/2002	Heil et al.	2004/0089308 A1	5/2004	Welch	
2002/0137749 A1	9/2002	Levinson et al.	2004/0092494 A9	5/2004	Dudley	
2002/0142017 A1	10/2002	Simonnet	2004/0092583 A1	5/2004	Shanahan-Prendergast	
2002/0151530 A1	10/2002	Leonard et al.	2004/0093261 A1	5/2004	Jain et al.	
2002/0156394 A1	10/2002	Mehrotra et al.	2004/0131670 A1	7/2004	Gao	
2002/0169150 A1	11/2002	Pickar	2004/0138103 A1	7/2004	Patt	
2002/0169205 A1	11/2002	Chwalisz et al.	2004/0142012 A1	7/2004	Bunt et al.	
2002/0173510 A1	11/2002	Levinson et al.	2004/0146539 A1	7/2004	Gupta	
2002/0193356 A1	12/2002	Van Beek et al.	2004/0146894 A1	7/2004	Warrington et al.	
2002/0193758 A1	12/2002	Sandberg	2004/0161435 A1	8/2004	Gupta	
2002/0197286 A1	12/2002	Brandman et al.	2004/0176324 A1	9/2004	Salvati et al.	
2003/0003139 A1	1/2003	Lipp et al.	2004/0176336 A1	9/2004	Rodriguez	
2003/0004145 A1	1/2003	Leonard	2004/0185104 A1	9/2004	Piao et al.	
2003/0007994 A1	1/2003	Bunt et al.	2004/0191207 A1	9/2004	Lipari et al.	
2003/0027772 A1	2/2003	Breton	2004/0191276 A1	9/2004	Muni	
2003/0044453 A1	3/2003	Dittgen et al.	2004/0198706 A1	10/2004	Carrara et al.	
2003/0049307 A1	3/2003	Gyurik	2004/0210280 A1	10/2004	Liedtke	
2003/0064097 A1	4/2003	Patel et al.	2004/0213744 A1	10/2004	Lulla et al.	
2003/0064975 A1	4/2003	Koch et al.	2004/0219124 A1	11/2004	Gupta	
2003/0072760 A1	4/2003	Sirbasku	2004/0225140 A1	11/2004	Fernandez et al.	
2003/0073248 A1	4/2003	Roth et al.	2004/0234606 A1	11/2004	Levine et al.	
2003/0073673 A1	4/2003	Hesch	2004/0241219 A1	12/2004	Hille et al.	
2003/0077297 A1 *	4/2003	Chen	A61K 9/4808 424/400	2004/0243437 A1	12/2004	Grace et al.
				2004/0253319 A1	12/2004	Netke et al.
2003/0078245 A1	4/2003	Bennink et al.	2004/0259817 A1	12/2004	Waldon et al.	
2003/0091620 A1	5/2003	Fikstad et al.	2004/0266745 A1	12/2004	Schwanitz et al.	
2003/0091640 A1	5/2003	Ramanathan et al.	2005/0003003 A1	1/2005	Basu et al.	
2003/0092691 A1	5/2003	Besse et al.	2005/0004088 A1	1/2005	Hesch	
2003/0096012 A1	5/2003	Besse et al.	2005/0009800 A1	1/2005	Thumbeck et al.	
2003/0104048 A1	6/2003	Patel et al.	2005/0014729 A1	1/2005	Pulaski	
2003/0109507 A1	6/2003	Franke et al.	2005/0020550 A1	1/2005	Morris et al.	
2003/0113268 A1	6/2003	Buenafae et al.	2005/0020552 A1	1/2005	Aschkenasy et al.	
2003/0114420 A1	6/2003	Salvati et al.	2005/0021009 A1	1/2005	Massara et al.	
2003/0114430 A1	6/2003	MacLeod et al.	2005/0025833 A1	2/2005	Aschkenasy et al.	
2003/0124182 A1	7/2003	Shojaei et al.	2005/0031651 A1	2/2005	Gervais et al.	
2003/0124191 A1	7/2003	Besse et al.	2005/0042173 A1	2/2005	Besse et al.	
2003/0130558 A1	7/2003	Massara et al.	2005/0042268 A1	2/2005	Aschkenasy et al.	
2003/0144258 A1	7/2003	Heil et al.	2005/0048116 A1	3/2005	Straub et al.	
2003/0157157 A1	8/2003	Luo et al.	2005/0054991 A1	3/2005	Tobyn et al.	
2003/0166509 A1	9/2003	Edwards et al.	2005/0079138 A1	4/2005	Chickering et al.	
2003/0170295 A1	9/2003	Kim et al.	2005/0085453 A1	4/2005	Govindarajan	
2003/0175329 A1	9/2003	Azarnoff et al.	2005/0101579 A1	5/2005	Shippen	
2003/0175333 A1	9/2003	Shefer et al.	2005/0113350 A1	5/2005	Duesterberg et al.	
2003/0180352 A1	9/2003	Patel et al.	2005/0118244 A1	6/2005	Theobald et al.	
2003/0181353 A1	9/2003	Nyce	2005/0118272 A1	6/2005	Besse et al.	
2003/0181728 A1	9/2003	Salvati et al.	2005/0129756 A1	6/2005	Podhaisky et al.	
2003/0191096 A1	10/2003	Leonard et al.	2005/0152956 A1	7/2005	Dudley	
2003/0195177 A1	10/2003	Leonard et al.	2005/0153946 A1	7/2005	Hirsh et al.	
2003/0215496 A1	11/2003	Patel et al.	2005/0164977 A1	7/2005	Coelingh	
2003/0219402 A1	11/2003	Rutter	2005/0182105 A1	8/2005	Nirschl et al.	
2003/0220297 A1	11/2003	Berstein et al.	2005/0186141 A1	8/2005	Gonda et al.	
2003/0224057 A1	12/2003	Martin-Letellier et al.	2005/0187267 A1	8/2005	Hamann et al.	
2003/0224059 A1	12/2003	Lerner et al.	2005/0192253 A1	9/2005	Salvati et al.	
2003/0225047 A1	12/2003	Caubel et al.	2005/0192310 A1	9/2005	Gavai et al.	
2003/0225048 A1	12/2003	Caubel et al.	2005/0196434 A1	9/2005	Briere	
2003/0225050 A1	12/2003	Grawe et al.	2005/0207990 A1	9/2005	Funke et al.	
2003/0228686 A1	12/2003	Klausner et al.	2005/0209209 A1	9/2005	Koch et al.	
2003/0229057 A1	12/2003	Caubel et al.	2005/0214384 A1	9/2005	Juturu et al.	
2003/0235596 A1	12/2003	Gao et al.	2005/0220825 A1	10/2005	Funke et al.	
2003/0236236 A1	12/2003	Chen et al.	2005/0220900 A1	10/2005	Popp et al.	
2004/0009960 A1	1/2004	Heil et al.	2005/0222106 A1	10/2005	Bracht	

US 11,033,626 B2

Page 7

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2005/0228692 A1	10/2005	Hodgdon	2007/0042038 A1	2/2007	Besse	
2005/0228718 A1	10/2005	Austin	2007/0060589 A1	3/2007	Purandare et al.	
2005/0239747 A1	10/2005	Yang et al.	2007/0066628 A1	3/2007	Zhang et al.	
2005/0239758 A1	10/2005	Roby	2007/0066637 A1	3/2007	Zhang et al.	
2005/0244360 A1	11/2005	Billoni	2007/0066675 A1	3/2007	Zhang et al.	
2005/0244522 A1	11/2005	Carrara et al.	2007/0078091 A1	4/2007	Hubler et al.	
2005/0245902 A1	11/2005	Cornish et al.	2007/0088029 A1	4/2007	Balog et al.	
2005/0250746 A1	11/2005	Iammatteo	2007/0093548 A1	4/2007	Diffendal et al.	
2005/0250750 A1	11/2005	Cummings et al.	2007/0116729 A1	5/2007	Palepu	
2005/0250753 A1	11/2005	Fink et al.	2007/0116829 A1	5/2007	Prakash et al.	
2005/0256028 A1	11/2005	Yun et al.	2007/0128263 A1	6/2007	Gargiulo et al.	
2005/0266078 A1	12/2005	Jorda et al.	2007/0154533 A1	7/2007	Dudley	
2005/0266088 A1	12/2005	Hinrichs et al.	2007/0167418 A1	7/2007	Ferguson	
2005/0271597 A1	12/2005	Keith	2007/0178166 A1	8/2007	Bernstein et al.	
2005/0271598 A1	12/2005	Friedman et al.	2007/0184558 A1	8/2007	Roth et al.	
2005/0272685 A1	12/2005	Hung	2007/0185068 A1	8/2007	Ferguson et al.	
2005/0272712 A1	12/2005	Grubb et al.	2007/0190022 A1	8/2007	Bacopoulos et al.	
2006/0009428 A1	1/2006	Grubb et al.	2007/0191319 A1	8/2007	Ke et al.	
2006/0014728 A1	1/2006	Chwalisz et al.	2007/0196415 A1	8/2007	Chen et al.	
2006/0018937 A1	1/2006	Friedman et al.	2007/0196433 A1	8/2007	Ron et al.	
2006/0019978 A1	1/2006	Balog et al.	2007/0207225 A1	9/2007	Squadrito	
2006/0020002 A1	1/2006	Salvati et al.	2007/0225281 A1	9/2007	Zhang et al.	
2006/0030615 A1	2/2006	Fensome et al.	2007/0232574 A1	10/2007	Galey et al.	
2006/0034889 A1	2/2006	Jo et al.	2007/0238713 A1	10/2007	Gast et al.	
2006/0034904 A1	2/2006	Weimann	2007/0243229 A1	10/2007	Smith et al.	
2006/0051391 A1	3/2006	Dvoskin et al.	2007/0248658 A1	10/2007	Zurdo et al.	
2006/0052341 A1	3/2006	Cornish et al.	2007/0254858 A1	11/2007	Cronk	
2006/0069031 A1	3/2006	Loumaye	2007/0255197 A1	11/2007	Humberstone et al.	
2006/0078618 A1	4/2006	Constantinides et al.	2007/0264309 A1	11/2007	Chollet et al.	
2006/0083778 A1	4/2006	Allison et al.	2007/0264345 A1	11/2007	Eros et al.	
2006/0084704 A1	4/2006	Shih et al.	2007/0264349 A1	11/2007	Lee et al.	
2006/0088580 A1	4/2006	Meconi et al.	2007/0286819 A1	12/2007	Devries et al.	
2006/0089337 A1	4/2006	Casper et al.	2007/0287688 A1	12/2007	Chan et al.	
2006/0093678 A1	5/2006	Chickering, III	2007/0287789 A1	12/2007	Jones et al.	
2006/0100180 A1	5/2006	Nubbemeyer et al.	2007/0298089 A1	12/2007	Saeki et al.	
2006/0106004 A1	5/2006	Brody et al.	2008/0026035 A1	1/2008	Chollet et al.	
2006/0110415 A1	5/2006	Gupta	2008/0026040 A1	1/2008	Farr et al.	
2006/0111424 A1	5/2006	Salvati et al.	2008/0026062 A1	1/2008	Farr et al.	
2006/0121102 A1	6/2006	Chiang	2008/0038219 A1	2/2008	Mosbaugh et al.	
2006/0121626 A1	6/2006	Imrich et al.	2008/0038350 A1	2/2008	Gerecke et al.	
2006/0134188 A1	6/2006	Podhaisky et al.	2008/0039405 A1	2/2008	Langley et al.	
2006/0135619 A1	6/2006	Kick et al.	2008/0050317 A1	2/2008	Tamarkin et al.	
2006/0165744 A1	7/2006	Jamil et al.	2008/0051351 A1	2/2008	Ghisalberti	
2006/0193789 A1	8/2006	Tamarkin et al.	2008/0063607 A1	3/2008	Tamarkin et al.	
2006/0194775 A1	8/2006	Tofovic et al.	2008/0069779 A1	3/2008	Tamarkin et al.	
2006/0204557 A1	9/2006	Gupta et al.	2008/0069791 A1	3/2008	Beissert	
2006/0233743 A1	10/2006	Kelly	2008/0085877 A1	4/2008	Bortz	
2006/0233841 A1	10/2006	Brodbeck et al.	2008/0095831 A1	4/2008	McGraw	
2006/0235037 A1	10/2006	Purandare et al.	2008/0095838 A1	4/2008	Abou	
2006/0240111 A1	10/2006	Fernandez et al.	2008/0113953 A1	5/2008	De Vries et al.	
2006/0246122 A1	11/2006	Langguth et al.	2008/0114050 A1	5/2008	Fensome et al.	
2006/0247216 A1	11/2006	Haj-Yehia	2008/0119537 A1	5/2008	Zhang et al.	
2006/0247221 A1	11/2006	Coelingh et al.	2008/0125402 A1	5/2008	Diliberti et al.	
2006/0251581 A1	11/2006	McIntyre et al.	2008/0138379 A1	6/2008	Jennings-Spring	
2006/0252049 A1	11/2006	Shuler et al.	2008/0138390 A1	6/2008	Hsu et al.	
2006/0257472 A1	11/2006	Nielsen	2008/0139392 A1	6/2008	Acosta-Zara et al.	
2006/0275218 A1	12/2006	Tamarkin et al.	2008/0145423 A1	6/2008	Khan et al.	
2006/0275360 A1	12/2006	Ahmed et al.	2008/0153789 A1	6/2008	Dmowski et al.	
2006/0276414 A1	12/2006	Coelingh et al.	2008/0175814 A1	7/2008	Phiasivongsa et al.	
2006/0280771 A1	12/2006	Groenewegen et al.	2008/0175905 A1	7/2008	Liu et al.	
2006/0280797 A1	12/2006	Shoichet et al.	2008/0175908 A1	7/2008	Liu et al.	
2006/0280800 A1	12/2006	Nagi et al.	2008/0188829 A1	8/2008	Creasy et al.	
2006/0292223 A1	12/2006	Woolfson et al.	2008/0206156 A1	8/2008	Cronk	
2007/0004693 A1	1/2007	Woolfson et al.	2008/0206159 A1	8/2008	Tamarkin et al.	
2007/0004694 A1	1/2007	Woolfson et al.	2008/0206161 A1	8/2008	Tamarkin et al.	
2007/0009559 A1	1/2007	Li et al.	2008/0214512 A1	9/2008	Seitz et al.	
2007/0009594 A1	1/2007	Grubb et al.	2008/0220069 A1	9/2008	Allison	
2007/0010550 A1	1/2007	McKenzie	2008/0226698 A1	9/2008	Tang et al.	
2007/0014839 A1	1/2007	Bracht	2008/0227763 A1	9/2008	Lanquetin et al.	
2007/0015698 A1	1/2007	Kleinman et al.	2008/0234199 A1	9/2008	Katamreddy	
2007/0021360 A1	1/2007	Nyce et al.	2008/0234240 A1	9/2008	Duesterberg et al.	
2007/0027201 A1	2/2007	McComas et al.	2008/0255078 A1	10/2008	Katamreddy	
2007/0031491 A1	2/2007	Levine et al.	2008/0255089 A1	10/2008	Katamreddy	
2007/0037780 A1	2/2007	Ebert et al.	2008/0261931 A1	10/2008	Hedner et al.	
2007/0037782 A1	2/2007	Hibino et al.	2008/0299220 A1	12/2008	Tamarkin et al.	

US 11,033,626 B2

Page 8

(56)

References Cited

U.S. PATENT DOCUMENTS

2008/0306036 A1	12/2008	Katamreddy	2010/0240626 A1	9/2010	Kulkarni et al.
2008/0312197 A1	12/2008	Rodriguez	2010/0247482 A1	9/2010	Cui et al.
2008/0312198 A1	12/2008	Rodriguez	2010/0247632 A1	9/2010	Dong et al.
2008/0319078 A1	12/2008	Katamreddy	2010/0247635 A1	9/2010	Rosenberg et al.
2009/0004246 A1	1/2009	Woolfson et al.	2010/0255085 A1	10/2010	Liu et al.
2009/0010968 A1	1/2009	Allart et al.	2010/0273730 A1	10/2010	Hsu et al.
2009/0011041 A1	1/2009	Musaeva et al.	2010/0278759 A1	11/2010	Murad
2009/0017120 A1	1/2009	Trimble et al.	2010/0279988 A1	11/2010	Setiawan et al.
2009/0022683 A1	1/2009	Song et al.	2010/0291191 A1	11/2010	Shoichet et al.
2009/0047357 A1	2/2009	Tomohira et al.	2010/0292199 A1	11/2010	Leverd et al.
2009/0053294 A1	2/2009	Prendergast	2010/0303825 A9	12/2010	Sirbasku
2009/0060982 A1	3/2009	Ron et al.	2010/0312137 A1	12/2010	Gilmour et al.
2009/0060997 A1	3/2009	Seitz et al.	2010/0316724 A1	12/2010	Whitfield et al.
2009/0068118 A1	3/2009	Eini et al.	2010/0322884 A1	12/2010	Dipietro et al.
2009/0074859 A1	3/2009	Patel	2010/0330168 A1	12/2010	Gicquel et al.
2009/0081206 A1	3/2009	Leibovitz	2011/0028439 A1	2/2011	Witt-Enderby et al.
2009/0081278 A1	3/2009	De Graaff et al.	2011/0039814 A1	2/2011	Huatan et al.
2009/0081303 A1	3/2009	Savoir et al.	2011/0053845 A1	3/2011	Levine et al.
2009/0092656 A1	4/2009	Klamerus et al.	2011/0066473 A1	3/2011	Bernick et al.
2009/0093440 A1	4/2009	Murad	2011/0076775 A1	3/2011	Stewart et al.
2009/0098069 A1	4/2009	Vacca	2011/0076776 A1	3/2011	Stewart et al.
2009/0099106 A1	4/2009	Phiasivongsa et al.	2011/0086825 A1	4/2011	Chatroux
2009/0099149 A1	4/2009	Liu et al.	2011/0087192 A1	4/2011	Uhland et al.
2009/0130029 A1	5/2009	Tamarkin et al.	2011/0091555 A1	4/2011	De Luigi Bruschi et al.
2009/0131385 A1	5/2009	Voskuhl	2011/0098258 A1	4/2011	Masini-Eteve et al.
2009/0137478 A1	5/2009	Bernstein et al.	2011/0098631 A1	4/2011	McIntyre et al.
2009/0137538 A1	5/2009	Klamerus et al.	2011/0104268 A1	5/2011	Pachot et al.
2009/0143344 A1	6/2009	Chang	2011/0104289 A1	5/2011	Savoir et al.
2009/0164341 A1	6/2009	Sunvold et al.	2011/0130372 A1	6/2011	Agostinacchio et al.
2009/0175799 A1	7/2009	Tamarkin et al.	2011/0135719 A1	6/2011	Besins et al.
2009/0181088 A1	7/2009	Song et al.	2011/0142945 A1	6/2011	Chen et al.
2009/0186081 A1	7/2009	Holm et al.	2011/0152840 A1	6/2011	Lee et al.
2009/0197843 A1	8/2009	Notelovitz et al.	2011/0158920 A1	6/2011	Morley et al.
2009/0203658 A1	8/2009	Marx et al.	2011/0171140 A1	7/2011	Illum et al.
2009/0214474 A1	8/2009	Jennings	2011/0182997 A1	7/2011	Lewis et al.
2009/0227023 A1	9/2009	Nichols et al.	2011/0190201 A1	8/2011	Hyde et al.
2009/0227550 A1	9/2009	Mattern	2011/0195031 A1	8/2011	Du
2009/0232897 A1	9/2009	Sahoo et al.	2011/0195114 A1	8/2011	Carrara et al.
2009/0258096 A1	10/2009	Cohen	2011/0195944 A1	8/2011	Mura et al.
2009/0264395 A1	10/2009	Creasy et al.	2011/0217341 A1	9/2011	Sah
2009/0269403 A1	10/2009	Shaked et al.	2011/0238003 A1	9/2011	Bruno-Raimondi et al.
2009/0285772 A1	11/2009	Phiasivongsa et al.	2011/0244043 A1	10/2011	Xu et al.
2009/0285869 A1	11/2009	Trimble	2011/0250256 A1	10/2011	Hyun-Oh et al.
2009/0318558 A1	12/2009	Kim et al.	2011/0250259 A1	10/2011	Buckman
2009/0324714 A1	12/2009	Liu et al.	2011/0250274 A1	10/2011	Shaked et al.
2009/0325916 A1	12/2009	Zhang et al.	2011/0256092 A1	10/2011	Phiasivongsa et al.
2010/0008985 A1	1/2010	Pellikaan et al.	2011/0262373 A1	10/2011	Umbert
2010/0028360 A1	2/2010	Atwood	2011/0262494 A1	10/2011	Achleitner et al.
2010/0034838 A1	2/2010	Staniforth et al.	2011/0268665 A1	11/2011	Tamarkin et al.
2010/0034880 A1	2/2010	Sintov et al.	2011/0275584 A1	11/2011	Wilckens et al.
2010/0040671 A1	2/2010	Ahmed et al.	2011/0281832 A1	11/2011	Li et al.
2010/0048523 A1	2/2010	Bachman et al.	2011/0287094 A1	11/2011	Penhasi et al.
2010/0055138 A1	3/2010	Margulies et al.	2011/0293720 A1	12/2011	General et al.
2010/0074959 A1	3/2010	Hansom et al.	2011/0294738 A1	12/2011	Ren et al.
2010/0086501 A1	4/2010	Chang et al.	2011/0300167 A1	12/2011	McMurry et al.
2010/0086599 A1	4/2010	Huempel et al.	2011/0301087 A1	12/2011	McBride et al.
2010/0092568 A1	4/2010	Lerner et al.	2011/0306579 A1	12/2011	Stein
2010/0105071 A1	4/2010	Laufer et al.	2011/0311592 A1	12/2011	Birbara
2010/0119585 A1	5/2010	Hille et al.	2011/0312927 A1	12/2011	Nachaegari et al.
2010/0129320 A1	5/2010	Phiasivongsa et al.	2011/0312928 A1	12/2011	Nachaegari et al.
2010/0136105 A1	6/2010	Chen et al.	2011/0318405 A1	12/2011	Erwin
2010/0137265 A1	6/2010	Leonard	2011/0318431 A1	12/2011	Gulati
2010/0137271 A1	6/2010	Chen et al.	2012/0009276 A1	1/2012	De Groote
2010/0143420 A1	6/2010	Shenoy et al.	2012/0015350 A1	1/2012	Nabatiyan et al.
2010/0143481 A1	6/2010	Shenoy et al.	2012/0021041 A1	1/2012	Rossi et al.
2010/0150993 A1	6/2010	Theobald et al.	2012/0028888 A1	2/2012	Janz et al.
2010/0152144 A1	6/2010	Hermsmeyer	2012/0028910 A1	2/2012	Combal et al.
2010/0168228 A1	7/2010	Bose et al.	2012/0028936 A1	2/2012	Gloger et al.
2010/0183723 A1	7/2010	Laurent-Applegate et al.	2012/0045532 A1	2/2012	Cohen
2010/0184736 A1	7/2010	Coelingh et al.	2012/0046264 A1	2/2012	Simes et al.
2010/0190758 A1	7/2010	Fauser et al.	2012/0046518 A1	2/2012	Yoakum et al.
2010/0204326 A1	8/2010	D'Souza	2012/0052077 A1	3/2012	Truitt, III et al.
2010/0210994 A1	8/2010	Zarif	2012/0058171 A1	3/2012	De Graaff et al.
2010/0221195 A1	9/2010	Tamarkin et al.	2012/0058962 A1	3/2012	Cumming et al.
2010/0227797 A1	9/2010	Axelson et al.	2012/0058979 A1	3/2012	Keith et al.
			2012/0064135 A1	3/2012	Levin et al.
			2012/0065179 A1	3/2012	Andersson
			2012/0065221 A1	3/2012	Babul
			2012/0087872 A1	4/2012	Tamarkin et al.

US 11,033,626 B2

Page 9

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2012/0101073 A1	4/2012 Mannion et al.	2013/0189230 A1	7/2013 Shoichet et al.			
2012/0121517 A1	5/2012 Song et al.	2013/0189368 A1	7/2013 Mosqueira et al.			
2012/0121692 A1	5/2012 Xu et al.	2013/0210709 A1	8/2013 McMurry et al.			
2012/0122829 A1	5/2012 Taravella et al.	2013/0216550 A1	8/2013 Penninger et al.			
2012/0128625 A1	5/2012 Shalwitz et al.	2013/0216596 A1	8/2013 Viladot et al.			
2012/0128654 A1	5/2012 Terpstra et al.	2013/0224177 A1	8/2013 Kim et al.			
2012/0128683 A1	5/2012 Shantha	2013/0224257 A1	8/2013 Sah et al.			
2012/0128733 A1	5/2012 Perrin et al.	2013/0224268 A1	8/2013 Alam et al.			
2012/0128777 A1	5/2012 Keck et al.	2013/0224300 A1	8/2013 Maggio			
2012/0129773 A1	5/2012 Geier et al.	2013/0225412 A1	8/2013 Sardari et al.			
2012/0129819 A1	5/2012 Vancaillie et al.	2013/0225542 A1	8/2013 Poegh et al.			
2012/0136013 A1	5/2012 Li et al.	2013/0226113 A1	8/2013 Schumacher et al.			
2012/0142645 A1	6/2012 Marx	2013/0243696 A1	9/2013 Wang et al.			
2012/0148670 A1	6/2012 Kim et al.	2013/0245253 A1	9/2013 Marx et al.			
2012/0149748 A1	6/2012 Shanler et al.	2013/0245570 A1	9/2013 Jackson			
2012/0172343 A1	7/2012 Lindenthal et al.	2013/0261096 A1	10/2013 Merian et al.			
2012/0184515 A1	7/2012 Klar et al.	2013/0266645 A1	10/2013 Becker et al.			
2012/0231052 A1	9/2012 Sitruk-Ware et al.	2013/0267485 A1	10/2013 Da Silva Maia Filho			
2012/0232011 A1	9/2012 Kneissel et al.	2013/0273167 A1	10/2013 Lee et al.			
2012/0232042 A1	9/2012 Klar et al.	2013/0274211 A1	10/2013 Burman et al.			
2012/0263679 A1	10/2012 Marlow et al.	2013/0280213 A1	10/2013 Voskuhl			
2012/0269721 A1	10/2012 Weng et al.	2013/0316374 A1	11/2013 Penninger et al.			
2012/0269878 A2	10/2012 Cantor et al.	2013/0317065 A1	11/2013 Tatani et al.			
2012/0277249 A1	11/2012 Andersson et al.	2013/0317315 A1	11/2013 Lu et al.			
2012/0277727 A1	11/2012 Doshi et al.	2013/0324565 A1	12/2013 Li et al.			
2012/0283671 A1	11/2012 Shibata et al.	2013/0331363 A1	12/2013 Li et al.			
2012/0295911 A1	11/2012 Mannion et al.	2013/0338122 A1	12/2013 Bernick et al.			
2012/0301517 A1	11/2012 Zhang et al.	2013/0338123 A1	12/2013 Bernick et al.			
2012/0301538 A1	11/2012 Gordon-Beresford et al.	2013/0338124 A1	12/2013 Li et al.			
2012/0302535 A1	11/2012 Caufriez et al.	2013/0345187 A1	12/2013 Rodriguez			
2012/0316130 A1	12/2012 Hendrix	2014/0018335 A1	1/2014 Tatani et al.			
2012/0316496 A1	12/2012 Hoffmann et al.	2014/0024590 A1	1/2014 Weidhaas et al.			
2012/0321579 A1	12/2012 Edelson et al.	2014/0031289 A1	1/2014 Song et al.			
2012/0322779 A9	12/2012 Voskuhl	2014/0031323 A1	1/2014 Perez			
2012/0328549 A1	12/2012 Edelson et al.	2014/0066416 A1	3/2014 Leunis et al.			
2012/0329738 A1	12/2012 Liu	2014/0072531 A1	3/2014 Kim et al.			
2013/0004619 A1	1/2013 Chow et al.	2014/0079686 A1	3/2014 Barman et al.			
2013/0011342 A1	1/2013 Tamarkin et al.	2014/0088051 A1	3/2014 Bernick et al.			
2013/0017239 A1	1/2013 Viladot et al.	2014/0088058 A1	3/2014 Maurizio			
2013/0022674 A1	1/2013 Dudley et al.	2014/0088059 A1	3/2014 Perumal et al.			
2013/0023505 A1	1/2013 Garfield et al.	2014/0094426 A1	4/2014 Drummond et al.			
2013/0023823 A1	1/2013 Simpson et al.	2014/0094440 A1	4/2014 Bernick et al.			
2013/0028850 A1	1/2013 Tamarkin et al.	2014/0094441 A1	4/2014 Bernick et al.			
2013/0029947 A1	1/2013 Nachaegari et al.	2014/0099362 A1	4/2014 Bernick et al.			
2013/0029957 A1	1/2013 Giliyan et al.	2014/0100159 A1	4/2014 Conrad			
2013/0045266 A1	2/2013 Choi et al.	2014/0100204 A1	4/2014 Bernick et al.			
2013/0045953 A1	2/2013 Sitruk-Ware et al.	2014/0100205 A1	4/2014 Bernick et al.			
2013/0059795 A1	3/2013 Lo et al.	2014/0100206 A1	4/2014 Bernick et al.			
2013/0064897 A1	3/2013 Binay	2014/0113889 A1	4/2014 Connor et al.			
2013/0072466 A1	3/2013 Choi et al.	2014/0127185 A1	5/2014 Stein et al.			
2013/0084257 A1	4/2013 Ishida et al.	2014/0127280 A1	5/2014 Duesterberg et al.			
2013/0085123 A1	4/2013 Li et al.	2014/0127308 A1	5/2014 Opara et al.			
2013/00889574 A1	4/2013 Schmidt-Gollwitzer et al.	2014/0128798 A1	5/2014 Janson et al.			
2013/0090318 A1	4/2013 Ullmann et al.	2014/0148491 A1	5/2014 Valia et al.			
2013/0102781 A1	4/2013 Bevill et al.	2014/0186332 A1	7/2014 Ezrin et al.			
2013/0108551 A1	5/2013 Langereis et al.	2014/0187487 A1	7/2014 Shoichet et al.			
2013/0116215 A1	5/2013 Coma et al.	2014/0193523 A1	7/2014 Henry			
2013/0116222 A1	5/2013 Arnold et al.	2014/0194396 A1	7/2014 Li et al.			
2013/0122051 A1	5/2013 Abidi et al.	2014/0206616 A1	7/2014 Ko et al.			
2013/0123175 A1	5/2013 Hill et al.	2014/0213565 A1	7/2014 Bernick et al.			
2013/0123220 A1	5/2013 Queiroz	2014/0288035 A1	9/2014 Hübner et al.			
2013/0123351 A1	5/2013 Dewitt	2014/0329783 A1	11/2014 Bernick et al.			
2013/0129818 A1	5/2013 Bernick et al.	2014/0335193 A1	11/2014 Rintoul et al.			
2013/0131027 A1	5/2013 Pakkalin et al.	2014/0370084 A1	12/2014 Bernick et al.			
2013/0131028 A1	5/2013 Snyder et al.	2014/0371182 A1	12/2014 Bernick et al.			
2013/0131029 A1	5/2013 Bakker et al.	2014/0371183 A1	12/2014 Bernick et al.			
2013/0149314 A1	6/2013 Bullerdiek et al.	2014/0371184 A1	12/2014 Bernick et al.			
2013/0164225 A1	6/2013 Tamarkin et al.	2014/0371185 A1	12/2014 Bernick et al.			
2013/0164346 A1	6/2013 Lee et al.	2015/0045335 A1	1/2015 Amadio			
2013/0165744 A1	6/2013 Carson et al.	2015/0133421 A1	2/2015 Bernick et al.			
2013/0178452 A1	7/2013 King	2015/0148323 A1	5/2015 Bernick et al.			
2013/0183254 A1	7/2013 Zhou et al.	2015/0202211 A1	5/2015 Cacace et al.			
2013/0183325 A1	7/2013 Bottoni et al.					
2013/0189193 A1	7/2013 Tamarkin et al.					
2013/0189196 A1	7/2013 Tamarkin et al.					

FOREIGN PATENT DOCUMENTS

EP	0275716 A1	7/1988
EP	0622075 A1	11/1994
EP	0785211 A1	7/1997

US 11,033,626 B2

Page 10

(56)	References Cited					
FOREIGN PATENT DOCUMENTS						
EP	0785212	A1	7/1997	WO	WO-2006034090	A1
EP	0811381	A1	12/1997	WO	WO-2006036899	A2
EP	0811381	B1	5/2003	WO	WO-2006053172	A2
EP	1094781	B1	7/2008	WO	WO-2007045027	A1
EP	2191833	A1	6/2010	WO	WO-2007103294	A2
EP	2191833	B1	2/2013	WO	WO-2006138735	A3
GB	452238	A	8/1936	WO	WO-2007120868	A2
GB	720561	A	12/1954	WO	WO-2007123790	A1
GB	848881	A	9/1960	WO	WO-2007124250	A2
GB	874368	A	8/1961	WO	WO-2007124250	A3
GB	1589946	A	5/1981	WO	WO-2007144151	A1
IN	216026		3/2008	WO	WO-2007103294	A3
IN	/53/KOL/2005		9/2009	WO	WO-2008049516	A3
IN	244217		11/2010	WO	WO-2008152444	A2
WO	WO-9011064	A1	10/1990	WO	WO-2009002542	A1
WO	WO-9317686	A1	9/1993	WO	WO-2009036311	A1
WO	WO-9422426	A1	10/1994	WO	WO-2009040818	A1
WO	WO-9530409	A1	11/1995	WO	WO-2008152444	A3
WO	WO-9609826	A2	4/1996	WO	WO-2009069006	A2
WO	WO-9619975	A1	7/1996	WO	WO-2009098072	A2
WO	WO-9630000	A1	10/1996	WO	WO-2009098072	A3
WO	WO-9705491	A1	2/1997	WO	WO-2009069006	A3
WO	WO-9743989	A1	11/1997	WO	WO-2009133352	A2
WO	WO-9810293	A1	3/1998	WO	WO-2010033188	A2
WO	WO-9832465	A1	7/1998	WO	WO-2009133352	A3
WO	WO-9851280	A1	11/1998	WO	WO-2010146872	A1
WO	WO-9932072	A1	7/1999	WO	WO-2011000210	A1
WO	WO-9939700	A1	8/1999	WO	WO-2011073995	A2
WO	WO-9942109	A1	8/1999	WO	WO-2011073995	A3
WO	WO-9943304	A1	9/1999	WO	WO-2010033188	A3
WO	WO-9948477	A1	9/1999	WO	WO-2011120084	A1
WO	WO-9953910	A2	10/1999	WO	WO-2011128336	A1
WO	WO-9963974	A2	12/1999	WO	WO-2012009778	A2
WO	WO-0001351	A1	1/2000	WO	WO-2012024361	A1
WO	WO-0006175	A1	2/2000	WO	WO-2012055814	A1
WO	WO-0038659	A1	7/2000	WO	WO-2012055840	A1
WO	WO-0045795	A2	8/2000	WO	WO-2012065740	A1
WO	WO-0050007	A1	8/2000	WO	WO-2012098090	A1
WO	WO-0059577	A1	10/2000	WO	WO-2012116277	A1
WO	WO-0076522	A1	12/2000	WO	WO-2012118563	A2
WO	WO-0137808	A1	5/2001	WO	WO-2012120365	A1
WO	WO-0154699	A1	8/2001	WO	WO-2012127501	A2
WO	WO-0160325	A1	8/2001	WO	WO-2012156561	A1
WO	WO-0207700	A2	1/2002	WO	WO-2012156822	A1
WO	WO-0211768	A1	2/2002	WO	WO-2012158483	A2
WO	WO-0222132	A2	3/2002	WO	WO-2012166909	A1
WO	WO-0240008	A2	5/2002	WO	WO-2012170578	A1
WO	WO-0241878	A2	5/2002	WO	WO-2013011501	A1
WO	WO-02053131	A1	7/2002	WO	WO-2012009778	A3
WO	WO-02078604	A2	10/2002	WO	WO-2013025449	A1
WO	WO-02078602	A3	2/2003	WO	WO-2013028639	A1
WO	WO-03028667	A2	4/2003	WO	WO-2013035101	A1
WO	WO-03041718	A1	5/2003	WO	WO-2013044067	A1
WO	WO-03041741	A1	5/2003	WO	WO-2013045404	A2
WO	WO-03068186	A1	8/2003	WO	WO-2013059285	A1
WO	WO-03077923	A1	9/2003	WO	WO-2013078422	A2
WO	WO-03082254	A1	10/2003	WO	WO-2013063279	A1
WO	WO-03092588	A2	11/2003	WO	WO-2013064620	A1
WO	WO-2004014397	A1	2/2004	WO	WO-2013071281	A1
WO	WO-2004014432	A1	2/2004	WO	WO-2013088254	A1
WO	WO-2004017983	A1	3/2004	WO	WO-2013102665	A1
WO	WO-2004032897	A2	4/2004	WO	WO-2013106437	A1
WO	WO-2004052336	A2	6/2004	WO	WO-2013113690	A1
WO	WO-2004054540	A2	7/2004	WO	WO-2013124415	A1
WO	WO-2004080413	A2	9/2004	WO	WO-2013127727	A1
WO	WO-2005027911	A1	3/2005	WO	WO-2013127728	A1
WO	WO-2005030175	A1	4/2005	WO	WO-2013144356	A1
WO	WO-2005081825	A2	9/2005	WO	WO-2013149258	A2
WO	WO-2005087194	A1	9/2005	WO	WO-2013158454	A2
WO	WO-2005087199	A2	9/2005	WO	WO-2013170052	A1
WO	WO-2005105059	A1	11/2005	WO	WO-2013178587	A1
WO	WO-2005115335	A1	12/2005	WO	WO-2013181449	A1
WO	WO-2005120470	A1	12/2005	WO	WO-2013192248	A1
WO	WO-2005120517	A1	12/2005	WO	WO-2013192249	A1
WO	WO-2006013369	A2	2/2006	WO	WO-2013192250	A1

US 11,033,626 B2

Page 11

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	WO-2013192251	A1	12/2013
WO	WO-2014001904	A1	1/2014
WO	WO-2014004424	A1	1/2014
WO	WO-2014009434	A1	1/2014
WO	WO-2014018569	A1	1/2014
WO	WO-2014018570	A1	1/2014
WO	WO-2014018571	A2	1/2014
WO	WO-2014018856	A1	1/2014
WO	WO-2014018932	A2	1/2014
WO	WO-2014031958	A1	2/2014
WO	WO-2014041120	A1	3/2014
WO	WO-2014052792	A1	4/2014
WO	WO-2014056897	A1	4/2014
WO	WO-2014066442	A2	5/2014
WO	WO-2014074846	A1	5/2014
WO	WO-2014076231	A1	5/2014
WO	WO-2014076569	A2	5/2014
WO	WO-2014081598	A1	5/2014
WO	WO-2014086739	A1	6/2014
WO	WO-2014093114	A1	6/2014
WO	WO-2014104784	A1	7/2014

OTHER PUBLICATIONS

- Abbas, M.A., et al., "Regression of Endometrial Implants Treated with Vitamin D3 in a Rat Model of Endometriosis," European Journal of Pharmacology 715(1-3):72-75, Elsevier Science, Netherlands (2013).
- Abitec, CapmuIMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmuIMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmuIMCM, Safley Data Sheet, 2011, Janesville, WI.
- Abitec, CapmuIMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmuIMPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Abitec Corporation Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2 pages (2013).
- Acarturk, F., "Mucoadhesive Vaginal Drug Delivery Systems," Recent patents on drug delivery & formulation 3(3):193-205, Bentham Science Publishers, United Arab Emirates (2009).
- Acog, McKinlay, et al., "Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists," Obstetrics & Gynecology Agog, No. 141, vol. 123(1), 202-216, (2014).
- Advisory Action dated Jan. 29, 2007 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Alabi, K. A., et al., "Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID," Fountain Journal of Natural and Applied Sciences 2(2):32-7, Osogbo (2013).
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, (2009).
- Alvarez, P., et al., "Ectopic Uterine Tissue as a Chronic Pain Generator," Neuroscience 225:269-282, Elsevier Science, United States (2012).
- Application Note JASCO CD Spectra of Pharmaceuticals Substances Steroids, 2 pages.
- Araya-Sibaja, A.M., et al., "Morphology Study of Progesterone Polymorphs Prepared by Polymer-induced Heteronucleation (Pihn)," Scanning 35(4):213-221, John Wiley & Sons, United States (2013).
- Araya-Sibaja, Andrea Manela, et al., "Chemical Properties of Progesterone Selected Refer," SciFinder, American Chemical Society & US National Library of Med, (2014).
- Araya-Sibaja, Andrea Manela, et al., "Polymorphism in Progesterone," SciFinder, pp. 1-46, American Chemical Society & US National Library of Med, (2014).
- Araya-Sibaja, Andrea Manela, et al., "Polymorphism in Progesterone Selected References," SciFinder, pp. 1-12, American Chemical Society & US National Library of Med, (2014).
- Araya-Sibaja., et al., "Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PiHn) method," Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, Informa Healthcare (2014).
- Archer, D.F., et al., "Effects of Ospemifene on the Female Reproductive and Urinary Tracts : Translation From Preclinical Models into Clinical Evidence," Menopause, Lippincott-Raven Publishers, United States (2014).
- Archer, F., et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study 9(1):21-31, (1992).
- Ashburn, A.D., et al., "Cardiovascular , Hepatic and Renal Lesions in Mice Receiving Cortisone , Estrone and Progesterone," The Yale Journal of Biology and Medicine 35:329-340, Yale Journal of Biology and Medicine, United States (1963).
- Azeem, A., et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug development and industrial pharmacy 35(5):525-547, Informa Healthcare, England (2009).
- Azure Pharma, Inc., "Elestrin—estradiol gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, (2009).
- Bakhmutova-Albert, Ekaterina, et al., "Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization," SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, S., et al., "On the Stability of Salivary Progesterone Under Various Conditions of Storage," Steroids 46(6):967-974, Elsevier, United States (1985).
- Barnett. and Steven, M., "Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring," Vibrational Spectroscopy, vol. 8, pp. 263, (1995).
- Bartosova, L. and Bajgar, J., "Transdermal Drug Delivery in Vitro Using Diffusion Cells," Current Medicinal Chemistry 19(27):4671-4677, Bentham Science Publishers, Netherlands (2012).
- Benbow, A.L. and Waddell, B.J., "Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus During Rat Pregnancy," Biology of Reproduction 52(6):1327-1333, Society for the Study of Reproduction, United States (1995).
- Bernabei, M.T., et al., "[Release of Polymorphic forms of Progesterone From Dimethylpolysiloxane Matrices]," Bollettino chimico farmaceutico 122(1):20-26, Societa Editoriale Farmaceutica, Italy (1983).
- Bernard, et al., "Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol," Acta Crystallographica B28 :1349, (1972).
- Bernard Hospital and Michel Busetta, "Structure Cristalline et Moleculair de l'Oestradiol Hemihydrate," Acta Crystallographica B28 :560-567, (1972).
- Bhavnani, B.R. and Stanczyk, F.Z., "Misconception and Concerns About Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," The Journal of clinical endocrinology and metabolism 97(3):756-759, Endocrine Society, United States (2012).
- Bhavnani, B.R. and Stanczyk, F.Z., "Pharmacology of Conjugated Equine Estrogens: Efficacy, Safety and Mechanism of Action," The Journal of steroid biochemistry and molecular biology 142:16-29, Pergamon, England (2014).
- Bhavnani, B.R., et al., "Structure Activity Relationships and Differential interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (Ers) Eralpha and Erbeta," Endocrinology 149(10):4857-4870, Endocrine Society, United States (2008).
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Blake, E.J., et al., "Single and Multidose Pharmacokinetic Study of a Vaginal Micronized Progesterone insert (Endometrin) Compared with Vaginal Gel in Healthy Reproductive-Aged Female Subjects," Fertility and Sterility 94(4):1296-1301, Elsevier for the American Society for Reproductive Medicine, United States (2010).
- Borka. and Laszlo., Crystal Polymorphism of Pharmaceuticals, Acta Pharmaceutica Jugoslavia 40:71-94, (1990).
- Brandstatter-Kuhnert, M., Kofler A., "Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone," Microchimica Acta 6:847-853, Springer-Verlag, Germany (1959).

US 11,033,626 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- Brader Christensson, J., et al., "Positive Patch Test Reactions to Oxidized Limonene: Exposure and Relevance," *Contact Dermatitis* 71(5):264-272, Wiley, England (2014).
- Brinton, L.A. and Felix, A.S., "Menopausal Hormone Therapy and Risk of Endometrial Cancer" *The Journal of steroid biochemistry and molecular biology* 142:83-89, Pergamon, England (2014).
- "British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, accessed at <http://www.pharmacopoeia.co.uk/lbp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM]."
- Burry, K.A., et al., "Percutaneous Absorption of Progesterone in Postmenopausal Women Treated with Transdermal Estrogen," *American journal of obstetrics and gynecology* 180(6Pt1):1504-1511, Elsevier, United States (1999).
- Campsteyn, H., et al., "Structure Cristalline et Moléculaire de la Progesterone C21H3002," *Acta Crystallographica B28*:3032-3042, (1972).
- Cendejas-Santana, G., et al., "Growth and characterization of progesterone crystallites," *Revista Mexicana de Fisica* 50 S(1) : 1-3, (2004).
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Christen, R.D., et al., "Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin," *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 11(12):2417-2426, American Society of Clinical Oncology, United States (1993).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Differ in Allergenic Activity," *Contact Dermatitis* 59(6):344-352, Wiley, England (2008).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Show Specific Patch Test Reactions," *Contact Dermatitis* 70(5):291-299, Wiley, England (2014).
- Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," *Journal of Korean Pharmaceutical Sciences* 35(3):173-177, (2005).
- Cicinelli, E., et al., "Direct Transport of Progesterone From Vagina to Uterus," *Obstetrics and Gynecology* 95(3):403-406, Lippincott Williams & Wilkins, United States (2000).
- Committee of Obstetric Practice, Committee Opinion—No. 522, *Obstetrics & Gynecology*, 119(4):879-882, (2012).
- Commodari, F., et al., "Comparison of 17Beta-Estradiol Structures From X-Ray Diffraction and Solution Nmr," *Magnetic resonance in chemistry : MRC* 43(6):444-450, Wiley Heyden, England (2005).
- Cooper, A., et al., "Systemic Absorption of Progesterone From Progest Cream in Postmenopausal Women," *Lancet* 351(9111):1255-1256, Lancet Publishing Group, England (1998).
- International Search Report and written opinion for International Application No. PCT/US13/46442, dated Nov. 1, 2013.
- International Search Report and written opinion for International Application No. PCT/US13/46443, dated Oct. 31, 2013.
- International Search Report and written opinion for International Application No. PCT/US13/46444, dated Oct. 31, 2013.
- International Search Report and written opinion for International Application No. PCT/US13/46445, dated Nov. 1, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/023309, dated Apr. 9, 2013.
- International Search report for corresponding International Application No. PCT/US12/66406, dated Jan. 24, 2013.
- Corbett, S.H., et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina : Focus on Vulvodynia," *Southern Medical Journal* 107(7):433-436, Southern Medical Association, United States (2014).
- Corn Refiners Assoc. Com Oil, Edition 5, United States (2006).
- Crutchley, H.O., et al., "Estrogen Receptor Beta, but Not Estrogen Receptor Alpha, Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium," *The Journal of Clinical Endocrinology and Metabolism* 86(3):1370-1378, Endocrine Society, United States (2001).
- Dauqan, Eqbal M.A., et al., "Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil," *IPCBEE*, 14, IACSIT Press, Singapore (2011).
- Dideberg, O., et al., "Crystal data on progesterone (C21H3002), desoxycorticosterone (C21H3003), corticosterone (C21H3004) and aldosterone," *Journal of Applied Crystallography* 4:80, (1971).
- Diramio, J.A., et al., "Poly(Ethylene Glycol) Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," *Masters of Science Thesis*, University of Georgia, Athens, Georgia, 131 pages (2002).
- Diramio. "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," *The University of Georgia-Masters of Science Thesis*, http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1, , 131 pages, (2004).
- Drakulic, B.J., et al., "Role of Complexes formation Between Drugs and Penetration Enhancers in Transdermal Delivery," *International journal of pharmaceutics* 363(1-2):40-49, Elsevier/North-Holland Biomedical Press., Netherlands (2008).
- Du, J.Y., et al., "Percutaneous Progesterone Delivery via Cream or Gel Application in Postmenopausal Women : A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," *Menopause* 20(11):1169-1175, Lippincott-Raven Publishers, United States (2013).
- Duclos, R., et al., "Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing process. A calorimetric and radiocrystallographic study," *Journal of Thermal Analysis* 37:1869-1875, John Wiley & Sons, England (1991).
- Ebian, A.R., "Ebian Article: Polymorphism and solvation of ethinyl estradiol," *Pharmaceutica Acta Helveticae* 54(4):111-114, (1979).
- Eisenberger, A. and Westhoff, C., "Hormone Replacement Therapy and Venous Thromboembolism," *The Journal of steroid biochemistry and molecular biology* 142:76-82, Pergamon, England (2014).
- Engelhardt, H., et al., "Conceptus influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy," *Biology of Reproduction* 66(6):1875-1880, Society for the Study of Reproduction, United States (2002).
- Ettinger, B., et al., "Comparison of Endometrial Growth Produced by Unopposed Conjugated Estrogens or by Micronized Estradiol in Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 176(1 Pt1):112-117, Elsevier, United States (1997).
- Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GmbH, 28 pages (2010).
- Faassen, F., et al., "Physicochemical Properties and Transport of Steroids Across Caco-2 Cells," *Pharmaceutical research* 20(2):177-186, Kluwer Academic/Plenum Publishers, United States (2003).
- "FDA, Draft Guidance on Progesterone, accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>, accessed on (Recommended) Apr. 2010,(Revised) Feb. 2011."
- Ferrari, Roseli AP, et al., "Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters," *Scientia Agricola* 62(3):291-95, Piracicaba, brazil (2005).
- Filipsson,F., et al., "Concise International Chemical Assessment Document 5," Limonene, first draft, World Health Organization, Geneva, 36 pages (1998).
- Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002, filed Nov. 21, 2012.
- Final Office Action dated Oct. 26, 2012 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Flyvholm, M.A. and Menne, T., "Sensitizing Risk of butylated Hydroxytoluene Based on Exposure and Effect Data," *Contact Dermatitis* 23(5):341-345, Wiley, England (1990).
- Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," *Contraception* 54(2):59-69, Elsevier, United States (1996).
- Franklin, R.D. and Kutteh, W.H., "Characterization of Immunoglobulins and Cytokines in Human Cervical Mucus : influence of Exogenous and Endogenous Hormones," *Journal of Reproductive Immunology* 42(2):93-106, Elsevier/North-Holland Biomedical Press, Ireland (1999).

US 11,033,626 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Franz, T.J., et al., "Use of Excised Human Skin to Assess the Bioequivalence of Topical Products," *Skin Pharmacology and Physiology* 22(5):276-286, Karger, Switzerland (2009).
- Freedman, R.R., "Menopausal Hot Flashes: Mechanisms, Endocrinology, Treatment," *The Journal of steroid biochemistry and molecular biology* 142:115-120, Pergamon, England (2014).
- Fuchs, K.O., et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Aesthetic Dermatology* 8(1):14-19, (2006).
- Fuchs, K.O., et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Cutis* 71(6):481-488, Frontline Medical Communications, United States (2003).
- Fuchs, K.O., et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Pharmacology/Cosmetology* 5(1), (2006).
- Fugh-Berman, A. and Bythrow, J., "Bioidentical Hormones for Menopausal Hormone Therapy: Variation on A Theme," *Journal of general internal medicine* 22(7):1030-1034, Springer, United States (2007).
- Furness, S., et al., "Hormone therapy in Postmenopausal Women and Risk of Endometrial Hyperplasia," *The Cochrane Database of Systematic Reviews* 8:1-204, Wiley, England (2012).
- Gafvert, E., et al., "Free Radicals in Antigen formation: Reduction of Contact Allergic Response to Hydroperoxides by Epidermal Treatment with Antioxidants," *The British Journal of Dermatology* 146(4):649-656, Blackwell Scientific Publications, England (2002).
- Ganem-Quintamar, et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," *International Journal of Pharmaceutics*, 147(2):165-171, (1997) Abstract Only.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 6 pages (2012).
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 5 pages (2012).
- Gattefossé, "Excipients for Safe and Effective Topical Delivery," <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#> (2012).
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 8 pages 2012.
- Gillet, J.Y., et al., "Induction of Amenorrhea During Hormone Replacement therapy : Optimal Micronized Progesterone Dose A Multicenter Study," *Maturitas* 19(2):103-115, Elsevier/North Holland Biomedical Press, Ireland (1994).
- Giron, D., "Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates," *Thermochimica Acta* 248:1-59, Elsevier B.V., Netherlands (1995).
- Giron-Forest, D., et al., "Thermal Analysis Methods for Pharmacopoeial Materials," *Journal of pharmaceutical and biomedical analysis* 7(12):1421-1433, Elsevier Science, England (1989).
- Glaser, R.L., et al., "Pilot Study : Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina," *Gynecologic and Obstetric Investigation* 66(2):111-118, Basel, New York, Karger., Switzerland (2008).
- Golatowski, C., et al., "Comparative Evaluation of Saliva Collection Methods for Proteome Analysis," *International Journal of Clinical Chemistry* 41:42-46, Elsevier, Netherlands (2013).
- Graham, J.D. and Clarke, C.L., "Physiological Action of Progesterone in Target Tissues," *Endocrine Reviews* 18(4):502-519, Endocrine Society, United States (1997).
- Groothuis, P.G., et al., "Estrogen and the Endometrium : Lessons Learned From Gene Expression Profiling in Rodents and Human," *Human Reproduction Update* 13(4):405-417, Published for the European Society of Human Reproduction and Embryology by Oxford University Press, England (2007).
- Gunstone, Frank, D., et al., "Vegetable Oils in Food Technology: Composition, Properties and Uses," Blackwell Publishing, CRC Press, (2002).
- Gurney, E.P., et al., "The Women's Health initiative Trial and Related Studies: 10 Years Later: A Clinician's View," *The Journal of steroid biochemistry and molecular biology* 142:42105, Pergamon, England (2014).
- Hamid, K.A., et al., "The Effects of Common Solubilizing Agents on the intestinal Membrane Barrier Functions and Membrane Toxicity in Rats," *International Journal of Pharmaceutics* 379(1):100-108, Amsterdam, Elsevier/North-Holland Biomedical Press., Netherlands (2009).
- Hapgood, J.P., et al., "Potency of Progestogens Used in Hormonal Therapy: Toward Understanding Differential Actions," *The Journal of steroid biochemistry and molecular biology* 142:39-47, Pergamon, England (2014).
- Hargrove, J.T., et al., "Menopausal Hormone Replacement Therapy with Continuous Daily Oral Micronized Estradiol and Progesterone," *Obstetrics and gynecology* 73(4):606-612, Lippincott Wilkins, United States (1989).
- Harner B.A., and Norton, D.A., "Crystal data (I) for some pregnenes and pregnadienes," *Acta Crystallographica* 17:1610, (1964).
- Hatton, J., et al., "Safety and Efficacy of a Lipid Emulsion Containing Medium-Chain Triglycerides," *Clinical Pharmacy* 9(5):366-371, American Society of Hospital Pharmacists, United States (1990).
- He, F., et al., "Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia induced by Ovariectomy Combined with Estrogen," *Gynecologic and Obstetric Investigation* 76(1):51-56, Karger., Switzerland (2013).
- Helbling, I.M., et al., "The Optimization of an intravaginal Ring Releasing Progesterone Using a Mathematical Model," *Pharmaceutical research* 31(3):795-808, Kluwer Academic/Plenum Publishers, United States (2014).
- Helmy, A., et al., "Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats," *Clinical Pharmacology & Biopharmaceutics*, S2, 7 pages (2014).
- Henderson, V.W., "Alzheimer's Disease: Review of Hormone Therapy Trials and Implications for Treatment and Prevention After Menopause," *The Journal of steroid biochemistry and molecular biology* 142:99-106, Pergamon, England (2014).
- Henriksen, Thormod, et al., "An ENDOR Sturdy of Radiation-Induced Molecular Damage to Progesterone," *Journal of Magnetic Resonance* 63(2):333-342, Elsevier Inc., United States (1985).
- Hodis, H.N. and Mack, W.J., "Hormone Replacement Therapy and the association with Coronary Heart Disease and Overall Mortality: Clinical Application of the Timing Hypothesis," *The Journal of steroid biochemistry and molecular biology* 142:68-75, Pergamon, England (2014).
- Hospital, M., et al., "X-Ray Crystallography of Estrogens and Their Binding to Receptor Sites," *Molecular pharmacology* 8(4):438-445, American Society for Pharmacology and Experimental Therapeutics, United States (1972).
- Hostyniek, J., et al., "Predicting absorption of fragrance chemicals through human skin," *Journal of the Society of Cosmetic Chemists* 46:221-229, (1995).
- Hulsmann, S., et al., "Stability of Extruded 17 Beta-Estradiol Solid Dispersions," *Pharmaceutical Development and Technology* 6(2):223-229, Informa Healthcare, England (2001).
- Hurn, P.D. and Macrae, I.M., "Estrogen as a Neuroprotectant in Stroke," *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism* 20(4):631-652, Nature Publishing Group, United States (2000).
- Hyder, S.M., et al., "Synthetic Estrogen 17Alpha-Ethinodiol induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17Beta-Estradiol," *The Journal of Pharmacology and Experimental Therapeutics* 290(2):740-747, American Society for Pharmacology and Experimental Therapeutics, United States (1999).
- Johanson, G., "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," *Critical reviews in toxicology* 30(3):307-345, Informa Healthcare, England (2000).
- Johnson, S., Williams, and John, F.W. Keana , "Racemic Progesterone," *Tetrahedron Letters* 4(4):193-196, Pergamon Press Ltd., United Kingdom (1963).

US 11,033,626 B2

Page 14

(56)

References Cited

OTHER PUBLICATIONS

- Joshi, S.G., et al., "Detection and Synthesis of a Progestagen-Dependent Protein in Human Endometrium," *Journal of Reproduction and Fertility* 59(2):273-285, Portland Press, England (1980).
- Kanno J., et al., "The Oecd Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses : Phase 1," *Environmental Health Perspectives* 109(8):785-794, N. C. National Institute of Environmental Health Sciences., United States (2001).
- Karlberg, A.T., et al., "Air Oxidation of D-Limonene (the Citrus Solvent) Creates Potent Allergens," *Contact Dermatitis* 26(5):332-340, Wiley, England (1992).
- Karlberg, A.T., et al., "Influence of an Anti-Oxidant on the formation of Allergenic Compounds During Auto-Oxidation of D-Limonene," *The Annals of Occupational Hygiene* 38(2):199-207, Oxford University Press, England (1994).
- Kaunitz, A.M. "Extended Duration Use of Menopausal Hormone therapy," *Menopause* 21(6):679-681, Lippincott-Raven Publishers, United States (2014).
- Khalil, S.A.H., "Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions." *Drug Development and Industrial Pharmacy* 10(5):771-787, Marcel Dekker, New York (1984).
- Kharode, Y., et al., "The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention," *Endocrinology* 149(12):6084-6091, Endocrine Society, United States (2008).
- Kim, Y.W., et al., "Safety Evaluation and Risk Assessment of D-Limonene," *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 16(1):17-38, Informa Healthcare, England (2013).
- Kincl, F.A., et al., "Increasing Oral Bioavailability of Progesterone by formulation," *Journal of steroid biochemistry* 9(1):83-84, Pergamon Press, England (1978).
- Knuth., et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," *Advanced Drug Delivery Reviews*, 11(1-2):137-167, (1993) Abstract Only.
- Koga, K., et al., "Enhancing Mechanism of Labrasol on intestinal Membrane Permeability of the Hydrophilic Drug Gentamicin Sulfate." *European Journal of Pharmaceutics and Biopharmaceutics : Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik E.V* 64(1):82-91, Elsevier Science, Netherlands (2006).
- Komm, B.S., et al., "Bazedoxifene Acetate : A Selective Estrogen Receptor Modulator with Improved Selectivity," *Endocrinology* 146(9):3999-4008, Endocrine Society, United States (2005).
- Korkmaz, Filiz, "Biophysical Studies of Progesterone-Model Membrane Interactions," A Thesis Submitted to the Graduate School of Natural and Applied Sciences of the Middle East Technical University (2003).
- Kotiyan, P.N. and Vavia, P.R., "Stability indicating Hptlc Method for the Estimation of Estradiol," *Journal of pharmaceutical and biomedical analysis* 22(4):667-671, Elsevier Science, England (2000).
- Krzymintewski, R., et al., "EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone," *Journal of Magnetic Resonance* 46:300-305, Academic Press, England (1982).
- Kubli-Garfias, C., et al., "Ab initio calculations of the electronic structure of glucocorticoids," *Journal of Molecular Structure, Theochem* 454(2-3):267-275, Elsevier Science B.V., Netherlands (1998).
- Kubli-Garfias, Carlos, "Ab initio study of the electronic structure of progesterone and related progestins," *Journal of Molecular Structure, Theochem* 425(1-2):171-179, Elsevier B.V., Netherlands (1998).
- Kuhnert-Brandstaetter, M., Kofler, A., "Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II," 1:127-139, *Mikrochimica Acta* (1968).
- Kuhnert-Brandstaetter, M., Lnder, R., "Zur Hydratbildung bei Steroidhormonen," *Sci. Pharm.* 41(2):109-116, (1973).
- Kuhnert-Brandstaetter, M., "Thermo-microscopic and spectrophotometric: Determination of steroid hormones," *Microchemical Journal* 9:105-133, (1965).
- Kumasaka, T., et al., "Effects of Various forms of Progestin on the Endometrium of the Estrogen-Primed , Ovariectomized Rat," *Endocrine Journal* 41(2):161-169, Japan Endocrine Society, Japan (1994).
- Kuon, R.J. and Garfield, R.E., "Actions of Progestins for the inhibition of Cervical Ripening and Uterine Contractions to Prevent Preterm Birth," *Facts, Views & Vision in Obgyn* 4(2):110-119, Flemish Society of Obstetrics & Gynaecology, Belgium (2012).
- Kuon, R.J., et al., "A Novel Optical Method to Assess Cervical Changes During Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor," *American Journal of Obstetrics and Gynecology* 205(1):82.e15-82.e20, Elsevier, United States (2011).
- Kuon, R.J., et al., "Pharmacologic Actions of Progestins to inhibit Cervical Ripening and Prevent Delivery Depend on their Properties, the Route of Administration , and the Vehicle," *American Journal of Obstetrics and Gynecology* 202(5):455.e1-455.e9, Elsevier, United States (2010).
- Labrie, et al., "Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens," *Journal of Steroid Biochemistry & Molecular Biology* 138:359-367, Elsevier (2013).
- Lacey, J.V. Jr., "The Whi Ten Year's Later: An Epidemiologist's View," *The Journal of steroid biochemistry and molecular biology* 142:12-15, Pergamon, England (2014).
- Lahiani-Skiba, M., et al., "Solubility and Dissolution Rate of Progesterone-Cyclodextrin-Polymer Systems," *Drug development and industrial pharmacy* 32(9):1043-1058, Informa Healthcare, England (2006).
- Lancaster, R.W., et al., "The Polymorphism of Progesterone: Stabilization of a "Disappearing" Polymorph by Co-Crystallization," *Journal of pharmaceutical sciences* 96(12):3419-3431, Wiley-Liss, United States (2007).
- Land, Laura M., "The influence of water content of triglyceride oils on the solubility of steroids," *Pharmaceutical Research* 22(5):Springer Science+Business Media (2005).
- Lanigan, R.S. and Yamarik, T.A., "Final Report on the Safety Assessment of Bht (1)," *International Journal of Toxicology* 21(2):19-94, Sage Publications, United States (2002).
- Lapez-Belmonte, J., et al., "Comparative Uterine Effects on Ovariectomized Rats After Repeated Treatment with Different Vaginal Estrogen formulations," *Maturitas* 72(4):353-358, Elsevier/ North Holland Biomedical Press, Ireland (2012).
- Lauer, A.C., et al., "Evaluation of the Hairless Rat as a Model for in Vivo Percutaneous Absorption," *Journal of Pharmaceutical Sciences* 86(1):13-18, Wiley-Liss, United States (1997).
- Idder, Salima, et al., "Physicochemical properties of Progesterone," 1-26, American Chemical Society & U.S. National Library of Medicine (2014).
- Leonetti, H.B., et al., "Topical Progesterone Cream Has an Antiproliferative Effect on Estrogen-Stimulated Endometrium," *Fertility and sterility* 79(1):221-222, Elsevier for the American Society for Reproductive Medicine, United States (2003).
- Leonetti, H.B., et al., "Transdermal Progesterone Cream as an Alternative Progestin in Hormone therapy," *Alternative Therapies in Health and Medicine* 11(6):36-38, InnoVision Communications, United States (2005).
- Lewis, J.G., et al., "Caution on the Use of Saliva Measurements to Monitor Absorption of Progesterone From Transdermal Creams in Postmenopausal Women," *Maturitas* 41(1):1-6, Elsevier/North Holland Biomedical Press, Ireland (2002).
- Li, G.C., et al., "Solid-State Nmr Analysis of Steroidal Conformation of $17\bar{1}\pm$ - and $17\bar{1}^2$ -Estradiol in the Absence and Presence of Lipid Environment," *Steroids* 77(3):185-192, Elsevier, United States (2012).
- Lobo, R.A., "foreword: Hormone Therapy Arms," *The Journal of steroid biochemistry and molecular biology* 142:3, Pergamon, England (2014).

US 11,033,626 B2

Page 15

(56)

References Cited

OTHER PUBLICATIONS

- Lucy, et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle," *Biol Reprod* 35(2):300-11, (1986) Abstract Only.
- Lvova, M.S.H., et al., "Thermal Analysis in the Quality Control and Standardization of Some Drugs," *Journal of Thermal Analysis* 40:405-411, Wiley (1993).
- Madishetti, S.K., et al., "Development of Domperidone Bilayered Matrix Type Transdermal Patches : Physicochemical , in Vitro and Ex Vivo Characterization," *Journal of Faculty of Pharmacy* 18(3):221-229, BioMed Central, England (2010).
- Magness, R.R. and Ford, S.P., "Estrone, Estradiol-17 Beta and Progesterone Concentrations in Uterine Lymph and Systemic Blood Throughout the Porcine Estrous Cycle," *Journal of animal science* 57(2):449-455, American Society of Animal Science, United States (1983).
- "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," *Menopause* 20(9):888-902, Lippincott-Raven Publishers, United States (2013).
- McGuffey, Irena, "Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement," Catalent Pharma Solutions Somerset, NJ (2011).
- "Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014," <https://www.rsc.org/Merck-Index/monograph/mono1500003758/estradiol?q=unauthorize>.
- "Merck Index Online, Progesterone, Royal Society of Chemistry, accessed at <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>, accessed on 2013 search Feb. 17, 2014,".
- "Merck Index Online, Progesterone, Royal Society of Chemistry, accessed at <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>, accessed at 2013, search Feb. 24, 2014 .".
- Mesley, R.J., "Clathrate formation From Steroids," *Chemistry & industry* 37:1594-1595, John Wiley & Sons Ltd., England (1965).
- "Miao, Wenbin, et al.," Chemical Properties of Progesterone American Chemical Society & U.S. National Library of Medicine (2014).
- Miles, R.A., et al., "Pharmacokinetics and Endometrial Tissue Levels of Progesterone After Administration by intramuscular and Vaginal Routes : A Comparative Study," *Fertility and Sterility* 62(3):485-490, Elsevier for the American Society for Reproductive Medicine, United States (1994).
- Miller, J.A., et al., "Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast," *Journal of Cancer Therapy* 3(5A), Scientific Research Publishing, United States (2012).
- Mueck, A.O., et al., "Genomic and Non-Genomic Actions of Progestogens in the Breast," *The Journal of steroid biochemistry and molecular biology* 142:62-67, Pergamon, England (2014).
- Muramatsu, Mitsuo, "Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone," *Journal of Pharmaceutical Sciences* 68(2):175-178, American Pharmacists Association (1979).
- Ng, Jo-Han., et al., "Advances in biodiesel fuel for application in compression ignition engines," *Clean Technologies and Environmental Policy* 12:459-493, Springer-Verlag (2010).
- Nicklas, M., et al., "Preparation and Characterization of Marine Sponge Collagen Nanoparticles and Employment for the Transdermal Delivery of 17Beta-Estradiol-Hemihydrate," *Drug development and industrial pharmacy* 35(9):1035-1042, Informa Healthcare, England (2009).
- Nilsson, U., et al., "Analysis of Contact Allergenic Compounds in Oxidized d-Limonene," *Chromatographia* 42:199-205, (1996).
- Non Final Office Action dated Dec. 12, 2011 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545, filed Dec. 6, 2013.
- Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002, filed Nov. 21, 2012.
- Notelovitz, M., et al., "Initial 17Beta-Estradiol Dose for Treating Vasomotor Symptoms," *Obstetrics and Gynecology* 95(5):726-731, Lippincott Williams & Wilkins, United States (2000).
- Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002, filed Nov. 21, 2012.
- Notice of Allowance dated Sep. 11, 2013 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- NuGen, "What is NuGen HP Hair Growth System? ", <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, 3 pages, undated.
- NuGest 900™, <http://www.lhehormoneshop.net/nugest900.htm>, 4 pages, undated.
- O'Leary, P., et al., "Salivary, but Not Serum or Urinary Levels of Progesterone are Elevated After Topical Application of Progesterone Cream to Pre- and Postmenopausal Women," *Clinical Endocrinology* 53(5):615-620, Blackwell Scientific Publications, England (2000).
- "Open Notebook, Science Solubility Challenge, Solubility of progesterone in organic solvents, accessed at <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>, accessed on Jul. 16, 2013.",
- Opinion on Diethylene glycol monoethyl ether, Scientific Committee on Consumer Products, The SCCP adopted this opinion at its 10th plenary, 27 pages (2006).
- Otterson, K. "The Drug Quality and Security Act—Mind the Gaps," *The New England Journal of Medicine* 370(2):97-99, Massachusetts Medical Society., United States (2014).
- Palamakula, A., et al., "Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components" *Pharmaceutical Technology* 74-88, (2004).
- Panay, N., et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," DOI: 0.1177/1754045313489645, min.sagepub.com. *Menopause International: The Integrated Journal of Post reproductive Health* 0(0):1-10, (2013).
- Panay, N., et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," *Menopause international* 19(2):59-68, Sage, England (2013).
- Panay, N., et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Panchagnula, R. and Ritschel, W.A., "Development and Evaluation of an intracutaneous Depot formulation of Corticosteroids Using Transcutol as a Cosolvent: in-Vitro, Ex-Vivo and in-Vivo Rat Studies," *The Journal of pharmacy and pharmacology* 43(9):609-614, Wiley, England (1991).
- Parasuraman, S., et al., "Blood Sample Collection in Small Laboratory Animals," *Journal of Pharmacology & Pharmacotherapeutics* 1(2):87-93, Medknow Publications and Media, India (2010).
- Park, J.S., et al., "Solvent Effects on Physicochemical Behavior of Estradiols Recrystallized for Transdermal Delivery," *Archives of pharmaceutical research* 31(1):111-116, Pharmaceutical Society of Korea., Korea (South) (2008).
- Park, J.S., et al., "Use of Cp/Mas Solid-State Nmr for the Characterization of Solvate Molecules within Estradiol Crystal forms," *European journal of pharmaceutics and biopharmaceutics* 60(3):407-412, Elsevier Science, Netherlands (2005).
- Parrish, D.A. and Pinkerton, A.A., "A New Estra-1,3,5(10)-Triene-3,17Beta-Diol Solvate: Estradiol-Methanol-Water (3/2/1)," *Acta crystallographica. Section C, Crystal structure communications* 59(Pt2):o80-82, Wiley-Blackwell, United States (2003).
- Patel, et al., "Transdermal Drug Delivery System: A Review," *The Pharma Innovation, The Pharma Journal* 1(4), (2012).
- Payne, R.S., et al., "Examples of Successful Crystal Structure Prediction: Polymorphs of Primidone and Progesterone," *International Journal of Pharmaceutics* 177(2):231-245, Elsevier/North-Holland Biomedical Press., Netherlands (1999).
- PCCA, Apothogram, PCCA, Houston, TX, (2014).

US 11,033,626 B2

Page 16

(56)

References Cited

OTHER PUBLICATIONS

- Persson, Linda C, et al., "Physicochemical Properties of Progesterone Selecte," 1-5, American Chemical Society & U.S. National Library of Medicine (2014).
- Pfaus, J.G., et al., "Selective Facilitation of Sexual Solicitation in the Female Rat by a Melanocortin Receptor Agonist," Proceedings of the National Academy of Sciences of the United States of America 101(27):10201-10204, National Academy of Sciences, United States (2004).
- Pheasant, Richard, , "Polymorphism of 17-Ethinylestradiol," Schering Corporation, Bloomfield, NJ (1950).
- Pickles, V.R. "Cutaneous Reactions to injection of Progesterone Solutions into the Skin," British Medical Journal 2(4780):373-374, British Medical Association, England (1952).
- Pinkerton, J.V. and Thomas, S., "Use of Serms for Treatment in Postmenopausal Women," The Journal of Steroid Biochemistry and Molecular Biology 142:142-154, Pergamon, England (2014).
- Pinkerton, J.V. "What are the Concerns About Custom-Compounded "Bioidentical" Hormone therapy?," Menopause 21(12):1298-1300, Lippincott-Raven Publishers, United States (2014).
- Pisegna, Gisla L, "A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids," Thesis, McGill University, Dept. of Chem:National Library of Canada (1999).
- Prajapati, Hetal N., et al., "A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant UWATER," Springerlink.com, pp. 1-21, (2011).
- Prausnitz, M.R. and Langer, R., "Transdermal Drug Delivery," Nature Biotechnology 26(11):1261-1268, Nature America Publishing, United States (2008).
- Price, S.L. "The Computational Prediction of Pharmaceutical Crystal Structures and Polymorphism," Advanced drug delivery reviews 56(3):301-319, Elsevier Science Publishers, B.V., Netherlands (2004).
- Product Safety Assessment, Diethylene Glycol Monoethyl Ether, The Dow Chemical Company Page, 5 Pages (2007).
- Progynova TS 100, available online at file:I:/C:/Users/Caii%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%28Estradioi%20Hemihydrate%29.html, 2010.
- Provider Data Sheet, "About Dried Blood Spot Testing," ZRT Laboratory, 3 pages (2014).
- Rahn, D.D., et al., "Vaginal Estrogen for Genitourinary Syndrome of Menopause: A Systematic Review," Obstetrics and Gynecology 124(6):1147-1156, Lippincott Williams & Wilkins, United States (2014).
- Reisman, S.A., et al., "Topical Application of the Synthetic Triterpenoid Rta 408 Protects Mice From Radiation-induced Dermatitis," Radiation Research 181(5):512-520, Radiation Research Society, United States (2014).
- Restriction/Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623, filed Dec. 6, 2013.
- Restriction/Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562, filed Dec. 6, 2013.
- Rosilio, V., et al., "Physical Aging of Progesterone-Loaded Poly(D,L,-Lactide-Co-Glycolide) Microspheres," Pharmaceutical research 15(5):794-798, Kluwer Academic/Plenum Publishers, United States (1998).
- Ross, D., et al., "Randomized , Double-Blind , Dose-Ranging Study of the Endometrial Effects of a Vaginal Progesterone Gel in Estrogen-Treated Postmenopausal Women," American Journal of Obstetrics and Gynecology 177(4):937-941, Elsevier, United States (1997).
- Ruan, X. and Mueck, A.O., "Systemic Progesterone therapy—Oral, Vaginal , injections and Even Transdermal ?," Maturitas 79(3):248-255, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Salem, H.F. "Sustained-Release Progesterone Nanosuspension Following intramuscular injection in Ovariectomized Rats," International Journal of Nanomedicine 10:943-954,DOVE Medical Press, New Zealand (2010).
- Salole, E.G., "The Physicochemical Properties of Oestradiol," Journal of Pharmaceutical and Biomedical Analysis 5(7):635-648, Elsevier Science, England (1987).
- Salole, Eugene G., "Estradiol, Analytical Profiles of Drug Substances," vol. 15, pp. 283-318, (1986).
- Santen, R.J., "Menopausal Hormone Therapy and Breast Cancer," The Journal of Steroid Biochemistry and Molecular Biology 142:52-61, Pergamon, England (2014).
- Santen, R.J. "Vaginal Administration of Estradiol : Effects of Dose, Preparation and Timing on Plasma Estradiol Levels," The Journal of the International Menopause Society :1-14, Informa Healthcare, England (2014).
- Sarkar, Basu, et al., "Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal CreamTM and HRT CreamTM Base," Steroids and Hormonal Science 4:2, (2013).
- Sarrel, and Philip, "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," American Journal of Public Health, Research and Practice, pp. e1-e6, Published online ahead of print Jul. 18, 2013.
- Satyanarayana, D, et al., "Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids," Asian Journal of Chemistry 9(3): 418-26, (1997).
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, American Chemical Society (2014).
- Schindler, A.E., "The "Newer" Progestogens and Postmenopausal Hormone Therapy (Hrt)," The Journal of Steroid Biochemistry and Molecular Biology 142:48-51, Pergamon, England (2014).
- Schutte, S.C. and Taylor, R.N., "A Tissue—Engineered Human Endometrial Stroma That Responds to Cues for Secretory Differentiation , Decidualization , and Menstruation," Fertility and Sterility 97(4):997-1003, Elsevier for the American Society for Reproductive Medicine, United States (2012).
- Schweikart, K.M., et al., "Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats," Toxicologic Pathology 42(8):1188-1196, Sage Publications, United States (2014).
- SciFinder Scholar Prednisone Chemical Properties, SciFindre, pp. 1-7, National Library of Medicine (2014).
- SciFinder Scholar Prednisone Physical Properties, SciFinder, pp. 1-10, Natioinoal Library of Medicine (2014).
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, American Chemical Society (2014).
- Serantoni, Foresti, et al., "4-Pregnen-3, 20-Dione (progesterone, form II)," Crystal Structure Communications 4(1):189-92, CAPLUS Database (1975).
- Shao, R., et al., "Direct Effects of Metformin in the Endometrium : A Hypothetical Mechanism for the Treatment of Women with PCOS and Endometrial Carcinoma," Journal of Experimental & Clinical Cancer Research 33:41, BioMed Central, England (2014).
- Sharma, H.C., et al., "Physical Properties of Progesterone Selected Refer, SciFinder," pp. 1-5, American Chemical Society & U.S. National Library of Medicine (2014).
- Shrier, L.A., et al., "Mucosal Immunity of the Adolescent Female Genital Tract," The Journal of Adolescent Health 32(3):183-186, Elsevier, United States (2003).
- Shufelt, C.L., et al., "Hormone Therapy Dose , formulation , Route of Delivery , and Risk of Cardiovascular Events in Women : Findings From the Women's Health initiative Observational Study," Menopause 21(3):260-266, Lippincott-Raven Publishers, United States (2014).
- Siew, A, et al., "Bioavailability Enhancement with Lipid-Based Durg-Delivery Systems" Pharmaceutical Technology 28,30-31, (2014).
- Sigma-Aldrich, Progesterone—Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- Simon, J., et al., "Effective Treatment of Vaginal Atrophy with an Ultra-Low-Dose Estradiol Vaginal Tablet," Obstetrics and gynecology 112(5):1053-1060, Lippincott Williams & Wilkins, United States (2008).
- Simon, J.A. "What If the Women's Health initiative Had Used Transdermal Estradiol and Oral Progesterone instead?," Menopause 21(7):769-783, Lippincott-Raven Publishers, United States (2014).
- Sitruk-Ware, and Regine., "Oral Micronized Progesterone—Bioavailability Pharmacokinetics, Pharmacological and Therapeutic Implications—A Review," Contraception 36(4):373-402, (1987).

US 11,033,626 B2

Page 17

(56)

References Cited

OTHER PUBLICATIONS

- Sitruk-Ware, R., "Progestogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," *Menopause* 9(1):6-15, Lippincott-Raven Publishers, United States (2002).
- Smith and Nicholas., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens," *JAMA Intern Med.* pp. e1-e7, published online Sep. 30, 2013.
- Smyth, H.F., et al., "A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats," *Food and Cosmetics Toxicology* 2:641-642, Pergamon Press, England (1964).
- Stanczyk, F.Z. and Bhavnani, B.R., "Current Views of Hormone Therapy for the Management and Treatment of Postmenopausal Women," *The Journal of steroid biochemistry and molecular biology* 142:1-2, Pergamon, England (2014).
- Stanczyk, F.Z. and Bhavnani, B.R., "Use of Medroxyprogesterone Acetate for Hormone Therapy in Postmenopausal Women: Is It Safe?," *The Journal of steroid biochemistry and molecular biology* 142:30-38, Pergamon, England (2014).
- Stanczyk, F.Z., et al., "Ethinyl Estradiol and 17 β -Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk assessment," *Contraception* 87(6):706-727, Elsevier, United States (2013).
- Stanczyk, F.Z., et al., "Therapeutically Equivalent Pharmacokinetic Profile Across Three Application Sites for Ag200-15 , A Novel Low-Estrogen Dose Contraceptive Patch," *Contraception* 87(6):744-749, Elsevier, United States (2013).
- Stein, Emily A., et al., "Progesterone, SciFinder Scholar Search" 1-46, American Chemical Society & U.S. National Library of Medicine, Feb. 24, 2014.
- Stein, Emily A., et al., "Progesterone Physical Properties," 1-46, American Chemical Society & U.S. National Library of Medicine, Feb. 24, 2014.
- Stein, Emily A., et al., "Progesterone Physical Properties," 1-46, American Chemical Society & U.S. National Library of Medicine, Mar. 3, 2014.
- Strickley, R.G., "Solubilizing Excipients in Oral and injectable formulations," *Pharmaceutical research* 21(2):201-230, Kluwer Academic/Plenum Publishers, United States (2004).
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science* 47, pp. 36-39, (1981).
- Struhar, M., et al., "Preparation of the Estradiol Benzoate injection Suspension," *Ceskoslovenska farmacie* 27(6):245-249, Ceskoslovenska Lekarska Spolecnost, Czech Republic (1978).
- Sullivan, D.W.Jr., et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology* 72:40-50, Elsevier Science Ltd, England (2014).
- Sun, J. "D-Limonene : Safety and Clinical Applications," *Alternative Medicine Review* 12(3):259-264, Alternative Medicine Review, United States (2007).
- Tahition Noni. "Body Balance Cream," http://products.lni.com/dominican_republic/sa_spanish/nonistore/prodcul/3438/3416/, 1 page, undated.
- Tait, A.D., "Characterization of the Products From the Oxidation of Progesterone with Osmium Tetroxide," *Steroids* 20(5):531-542, Elsevier, United States (1972).
- Takacs, M., et al., "The Light Sensitivity of Corticosteroids in Crystalline form Photochemical Studies 59 (1)," *Pharmaceutica acta Helvetica* 66(5-6):137-140, Schweizerische Apotheker-Verein, Switzerland (1991).
- Tan, Melvin, S., et al., "A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025," Cedra Corporation, Austin.
- Tang, F.Y., et al., "Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat," *Biology of Reproduction* 31(2):399-413, Society for the Study of Reproduction, United States (1984).
- Tas, M., et al., "Comparison of Antiproliferative Effects of Metformine and Progesterone on Estrogen-induced Endometrial Hyperplasia in Rats," *Gynecological Endocrinology* 29(4):311-314, Informa Healthcare, England (2013).
- Tella, S.H., Gallagher, J.C., "Prevention and treatment of postmenopausal osteoporosis," *The Journal of Steroid Biochemistry and Molecular Biology* 142:155-170, Elsevier Ltd., United Kingdom (2014).
- Thomas, J., et al., "The Effect of Water Solubility of Solutes on Their Flux Through Human Skin in Vitro: An Extended Flynn Database Fitted to the Roberts-Sloan Equation," *International Journal of Pharmaceutics* 339(1-2):157-167, Elsevier/North-Holland Biomedical Press., Netherlands (2007).
- Thomas, P. "Characteristics of Membrane Progestin Receptor Alpha (Mpralpha) and Progesterone Membrane Receptor Component 1 (Pgmrc1) and their Roles in Mediating Rapid Progestin Actions," *Frontiers in Neuroendocrinology* 29(2):292-312, Academic Press, United States (2008).
- Tripathi, R., et al., "Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note," *AAPS PharmSciTech* 11(3):1493-1498, Elsevier/North-Holland Biomedical Press., Netherlands (2010).
- Trommer, H. and Neubert, R.H., "Overcoming the Stratum Corneum : the Modulation of Skin Penetration A Review," *Skin Pharmacology and Physiology* 19(2):106-121, Karger, Switzerland (2006).
- Tuleu, C., et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying formulation of Progesterone Presented in a Pellet and Liquid form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences* 93(6):1495-1502, Wiley-Liss, United States (2004).
- Ueda, T., et al., "Topical and Transdermal Drug Products," *Pharmacopeial Forum* 35(3):750-764, (2009).
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Suplementto USP36-NF 31, pp. 6141-6151, (2013).
- USP, Lauroyl Polyoxylglycerides, Safty Data Sheet, US, 5611 Version #02, pp. 1-9, (2013).
- "USP Monographs: Progesterone. USP29, accessed at www.pharmacopeia.cn/v29240/usp29nf24sO_m69870.html, accessed on Feb. 25, 2014.",
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, (2013).
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, (2013).
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, (2013).
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, (2013).
- USP, USP Certificate—Corn Oil, Lot GOL404, Jul. 2013.
- Utian, W.H., et al., "Relief of Vasomotor Symptoms and Vaginal Atrophy with Lower Doses of Conjugated Equine Estrogens and Medroxyprogesterone Acetate," *Fertility and sterility* 75(6):1065-1079, Elsevier for the American Society for Reproductive Medicine, United States (2001).
- Voegtlle, K.M. and Granger, D.A., "Dispatches From the interface of Salivary Bioscience and Neonatal Research," *Frontiers in Endocrinology* 5:25,Frontiers Research Foundation, Switzerland (2014).
- Waddell, B.J. and Bruce, N.W., "The Metabolic Clearance of Progesterone in the Pregnant Rat : Absence of a Physiological Role for the Lung," *Biology of Reproduction* 40(6):1188-1193, Society for the Study of Reproduction, United States (1989).
- Waddell, B.J. and Oleary, P.C., "Distribution and Metabolism of Topically Applied Progesterone in a Rat Model," *The Journal of Steroid Biochemistry and Molecular Biology* 80(4-5):449-455, Pergamon, England (2002).
- Walter, L.M., et al., "The Role of Progesterone in Endometrial Angiogenesis in Pregnant and Ovariectomised Mice," *Reproduction* 129(6):765-777,Reproduction and Fertility by BioScientifica, England (2005).
- Warney Cole and Percy L., Julian, "A Study of the 22-Ketosteroids," *Journal of the American Chemical Society* 67(8):1369-1375, (1945).
- Weber, E.J. "Corn Lipids," *Cereal Chemistry Journal* 55(5): 572-584, American Association of Cereal Chemists (1978).

US 11,033,626 B2

Page 18

(56)

References Cited**OTHER PUBLICATIONS**

- Weber, M.T., et al., "Cognition and Mood in Perimenopause: A Systematic Review and Meta-Analysis," *The Journal of Steroid Biochemistry and Molecular Biology* 142:90-98, Pergamon, England (2014).
- Whitehead, M.I., et al., "Absorption and Metabolism of Oral Progesterone," *British medical journal* 280(6217):825-827, British Medical Association, England (1980).
- William, L., Duax, Jane F., Griffin, Douglas, C., Rohrer, "Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations," *Journal of the American Chemical Society* 103(22):6705-6712, (1981).
- Wiranidchapong, Chutima et al., "Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate," *Thermochimica Acta* 485(1-2):57-64, Elsevier B.V., Netherlands (2009).
- Wood, C.E., et al., "Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys," *Breast Cancer Research and Treatment* 101:125-134, Springer Science+ Business Media B.V (2006), published online Jul. 14, 2006.
- Wren, B.G., et al., "Effect of Sequential Transdermal Progesterone Cream on Endometrium , Bleeding Pattern , and Plasma Progesterone and Salivary Progesterone Levels in Postmenopausal Women," *The Journal of the International Menopause Society* 3(3):155-160, Informa Healthcare, England (2000).
- Wu, X., et al., "Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus," *Biology of Reproduction* 69(4):1308-1317, Society for the Study of Reproduction, United States (2003).
- Yalkowsky, Samuel, H. , "Handbook of Acqueous Solubility Data," 1110-1111, CRC Press, United States.
- Yalkowsky, S.H. and Valvani, S.C., "Solubility and Partitioning I: Solubility of Nonelectrolytes in Water," *Journal of Pharmaceutical Sciences* 69(8):912-922, Wiley-Liss, United States (1980).
- Yue, W., et al., "Genotoxic Metabolites of Estradiol in Breast: Potential Mechanism of Estradiol induced Carcinogenesis," *The Journal of Steroid Biochemistry and Molecular Biology* 86(3-5):477-486, Pergamon, England (2003).
- Zava, D. "Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues" Script:4-5.
- Zava, D.T., et al., "Percutaneous absorption of progesterone," *Maturitas* 77:91-92, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Geelen, M.J.H., et al., "Dietary Medium-Chain Fatty Acids Raise and (n-3) Polyunsaturated Fatty Acids Lower Hepatic Triacylglycerol Synthesis in Rats," *The Journal of Nutrition* 125:2449-2456, American Institute of Nutrition, United States (1995).
- Herman, A and Herman, A.P., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," *Journal of Pharmacy and Pharmacology* 67(4):473-485, Royal Pharmaceutical Society, England (2014).
- Manson, J.E., et al., "Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials," *The Journal of the American Medical Association* 310:1353-1368, American Medical Association, United States (2013).
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 10 pages.
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Notice of Allowance, dated Dec. 15, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Feb. 11, 2015, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Notice of Allowance, dated Feb. 13, 2015, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Notice of Allowance, dated Jan. 22, 2015, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 5 pages.
- Notice of Allowance, dated Jul. 14, 2014, in U.S. Appl. No. 14/099,545, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Jul. 15, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 11 pages.
- Notice of Allowance, dated Nov. 26, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Notice of Allowance, dated Nov. 7, 2014, in U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, 14 pages.
- Office Action, dated Apr. 14, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Office Action, dated Apr. 7, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 10 pages.
- Office Action, dated Dec. 8, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 9 pages.
- Office Action, dated Feb. 18, 2015, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 8 pages.
- Office Action, dated Jul. 18, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jul. 2, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Office Action, dated Jul. 3, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 16 pages.
- Office Action, dated Jul. 30, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jun. 17, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 14 pages.
- Office Action, dated Mar. 12, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 24 pages.
- Office Action, dated Mar. 27, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Office Action, dated Oct. 1, 2014, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Office Action, dated Oct. 2, 2014, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Portman, D., et al., "One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy," *Menopause* 22(11): 7 pages, The North American Menopause Society, United States (2015).
- Rao, R. and Rao, S., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *Journal of Bioequivalence & Bioavailability* 6(4):139-143, Open Access (2014).
- Restriction Requirement, dated Apr. 14, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Apr. 29, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 7 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 9 pages.
- Restriction Requirement, dated Jul. 3, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 6 pages.
- Restriction Requirement, dated Mar. 16, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Mar. 20, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Mar. 26, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 7 pages.
- Restriction Requirement, dated Mar. 28, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 7 pages.
- International Search Report and Written Opinion of International Application No. PCT/US2015/023041, Korean Intellectual Property Office, Republic of Korea, dated Jun. 30, 2015, 14 pages.
- Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences* 11(3):42-49, NIPER, India (Jul.-Sep. 2010).

* cited by examiner

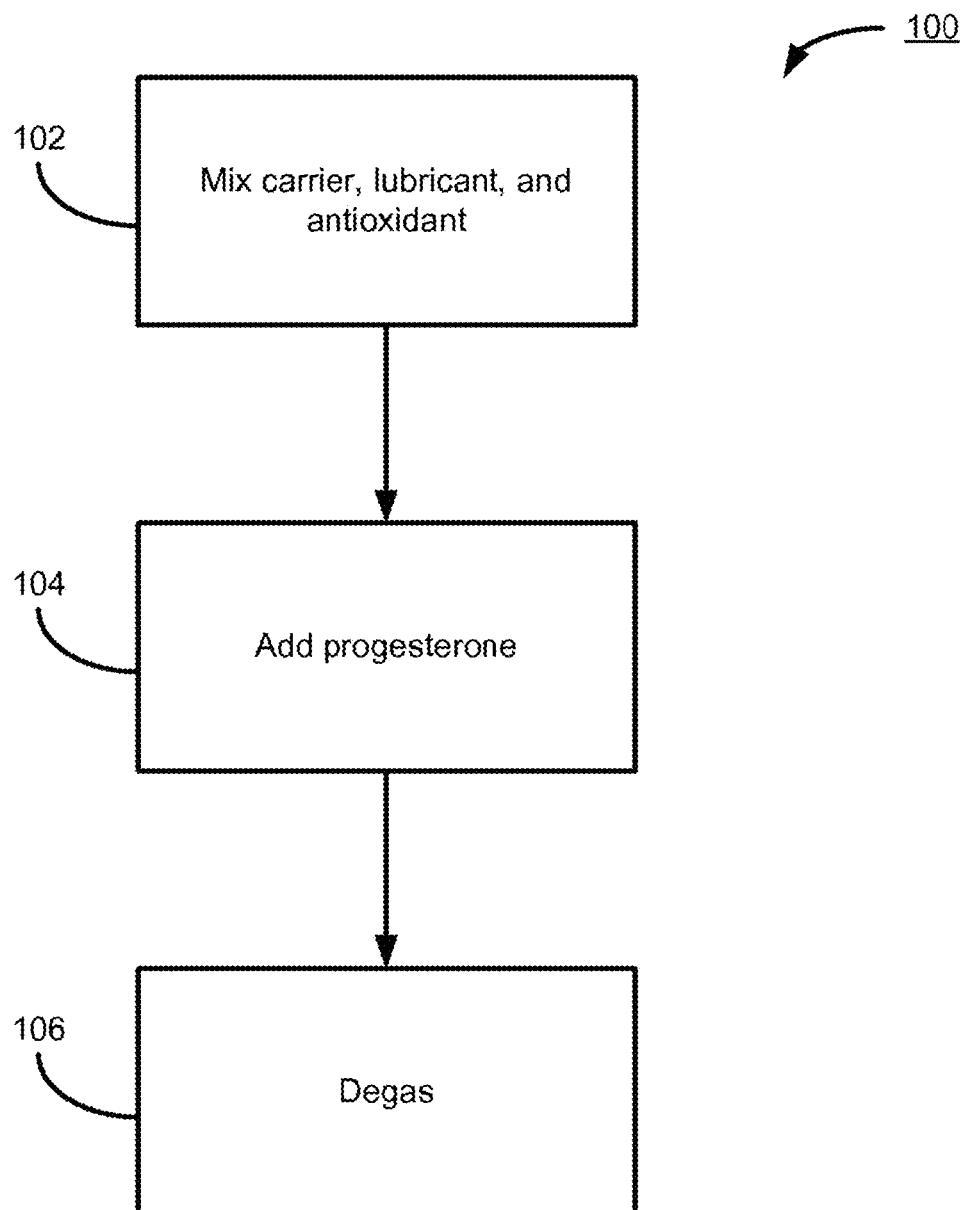
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Fig. 1



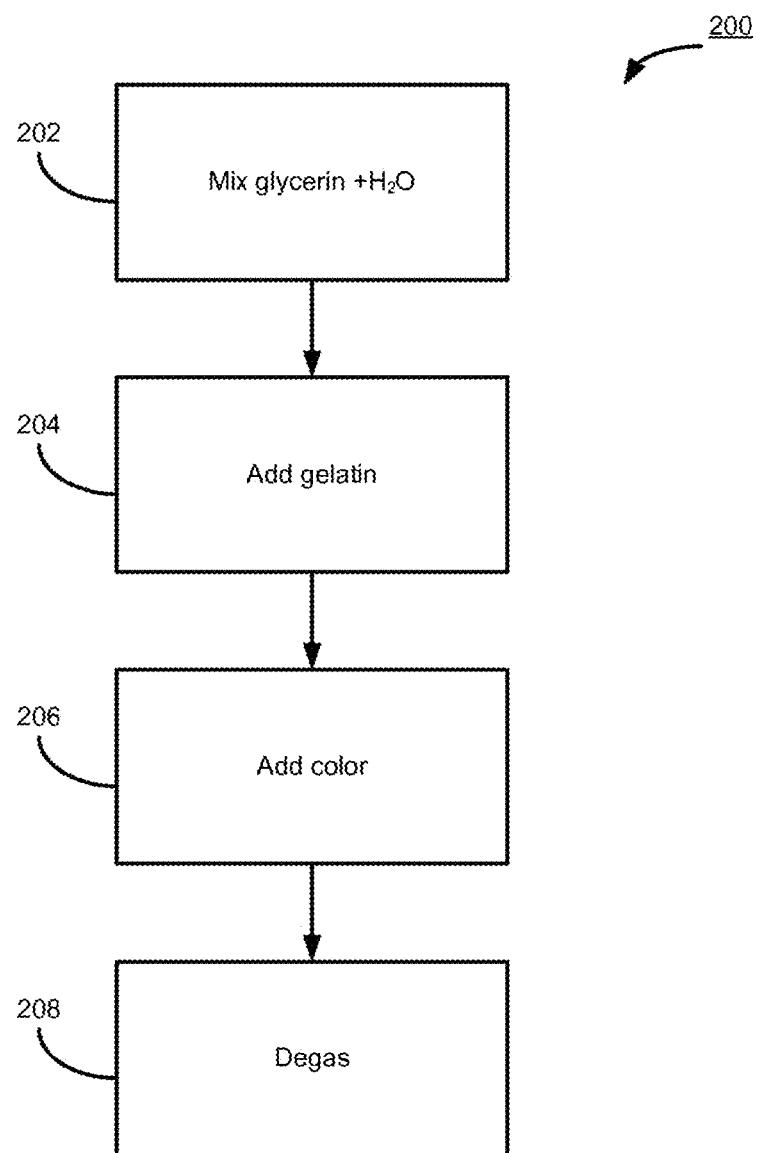
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Fig. 2



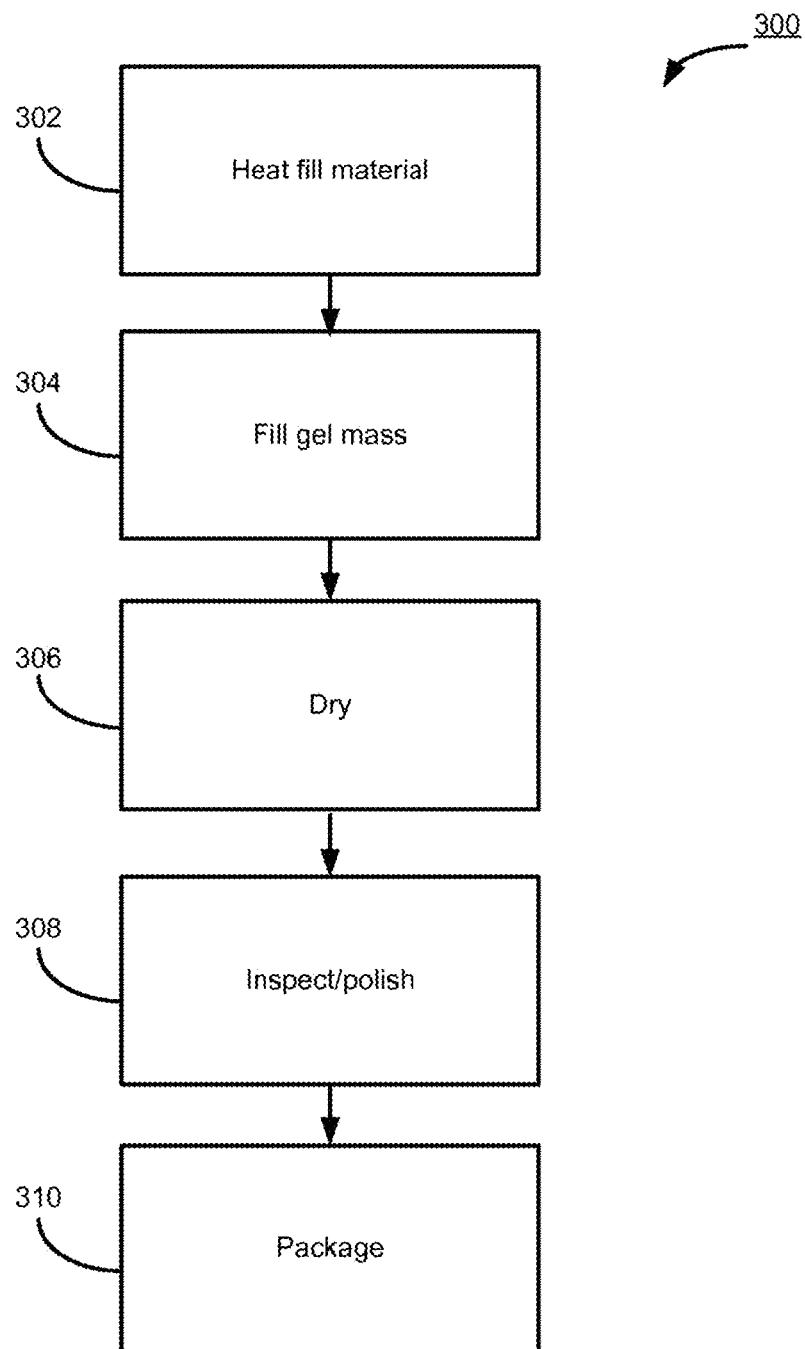
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Fig. 3



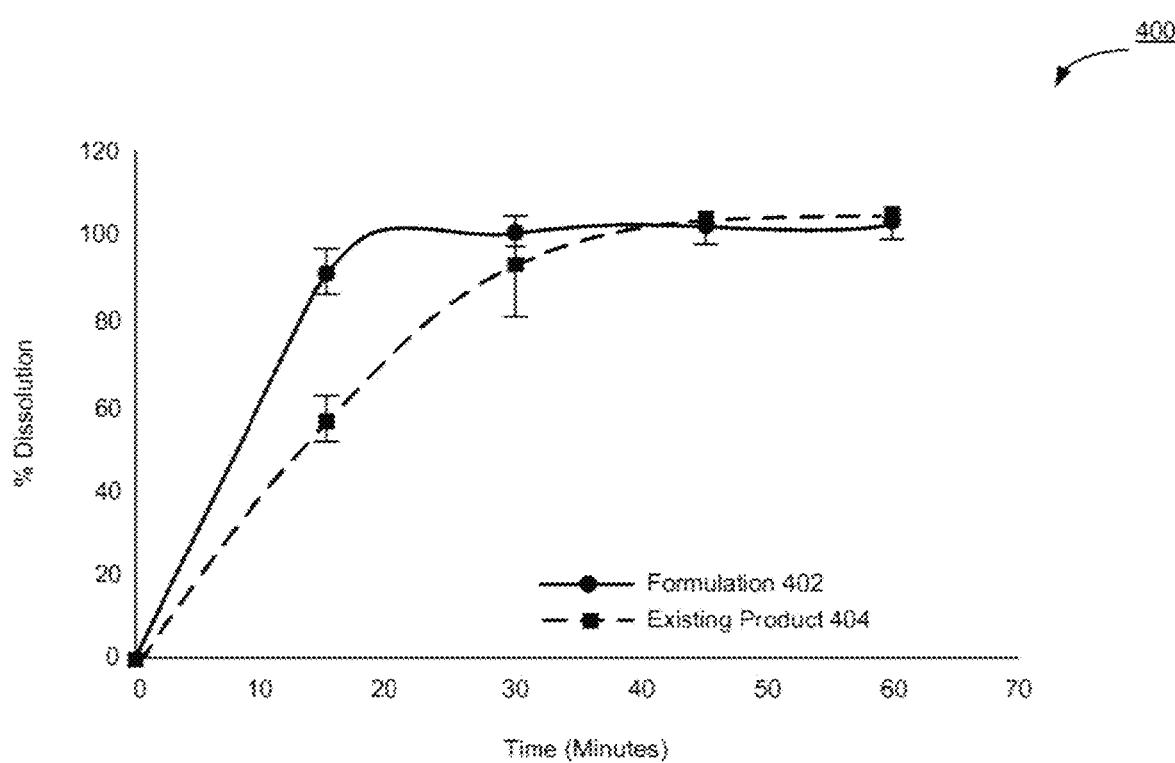
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Fig. 4



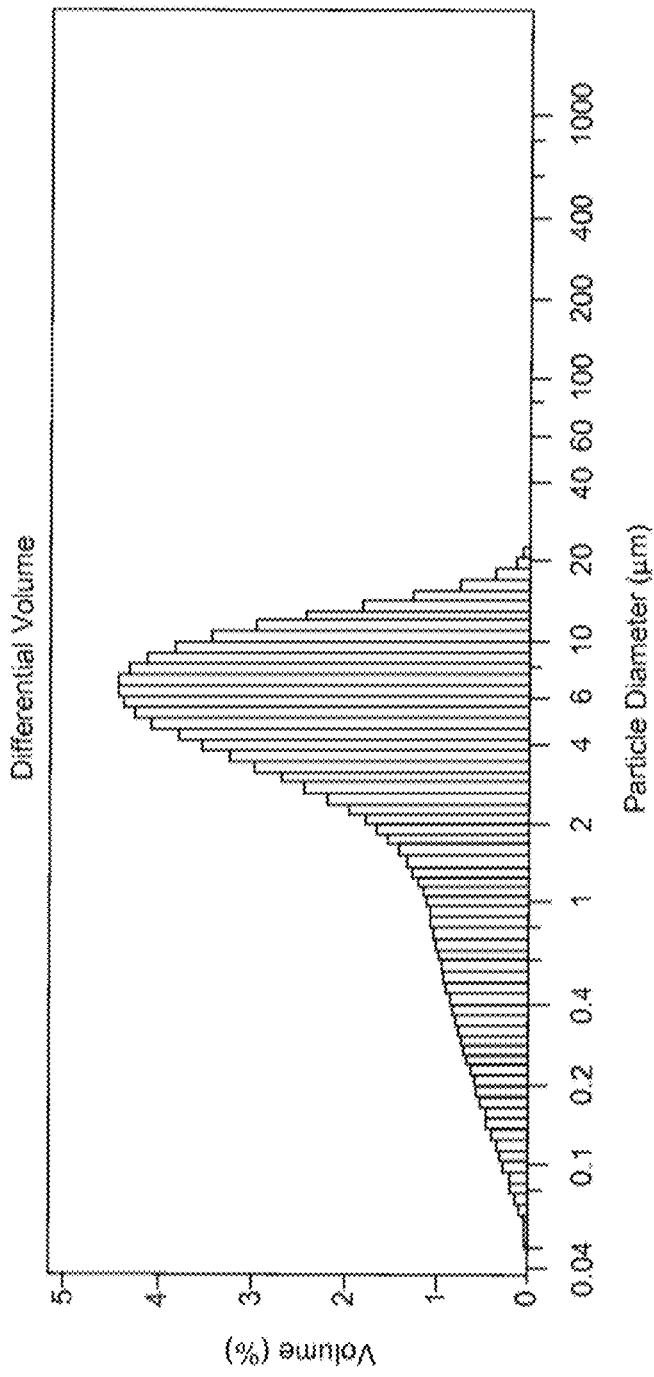
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Fig. 5



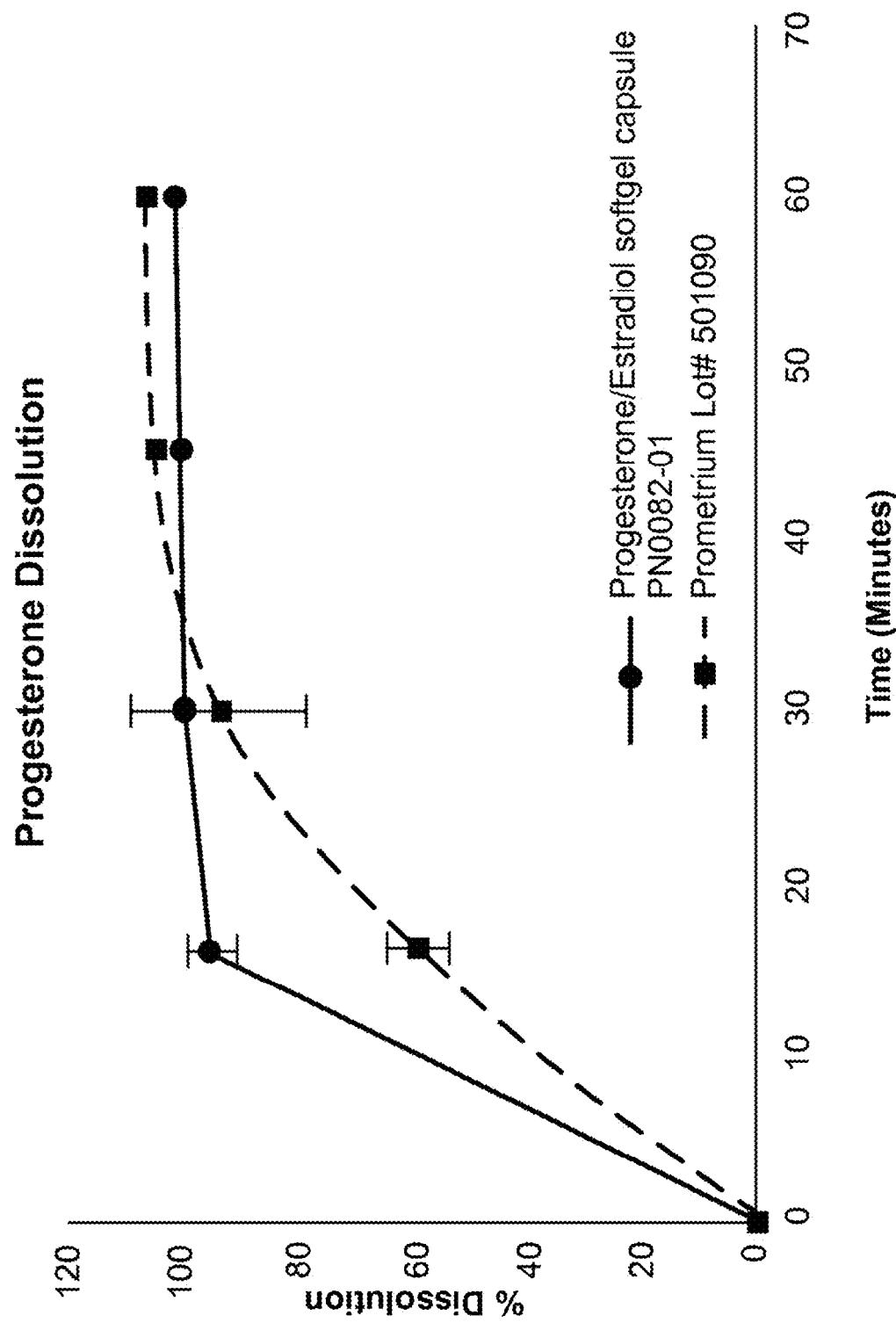
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Fig. 6



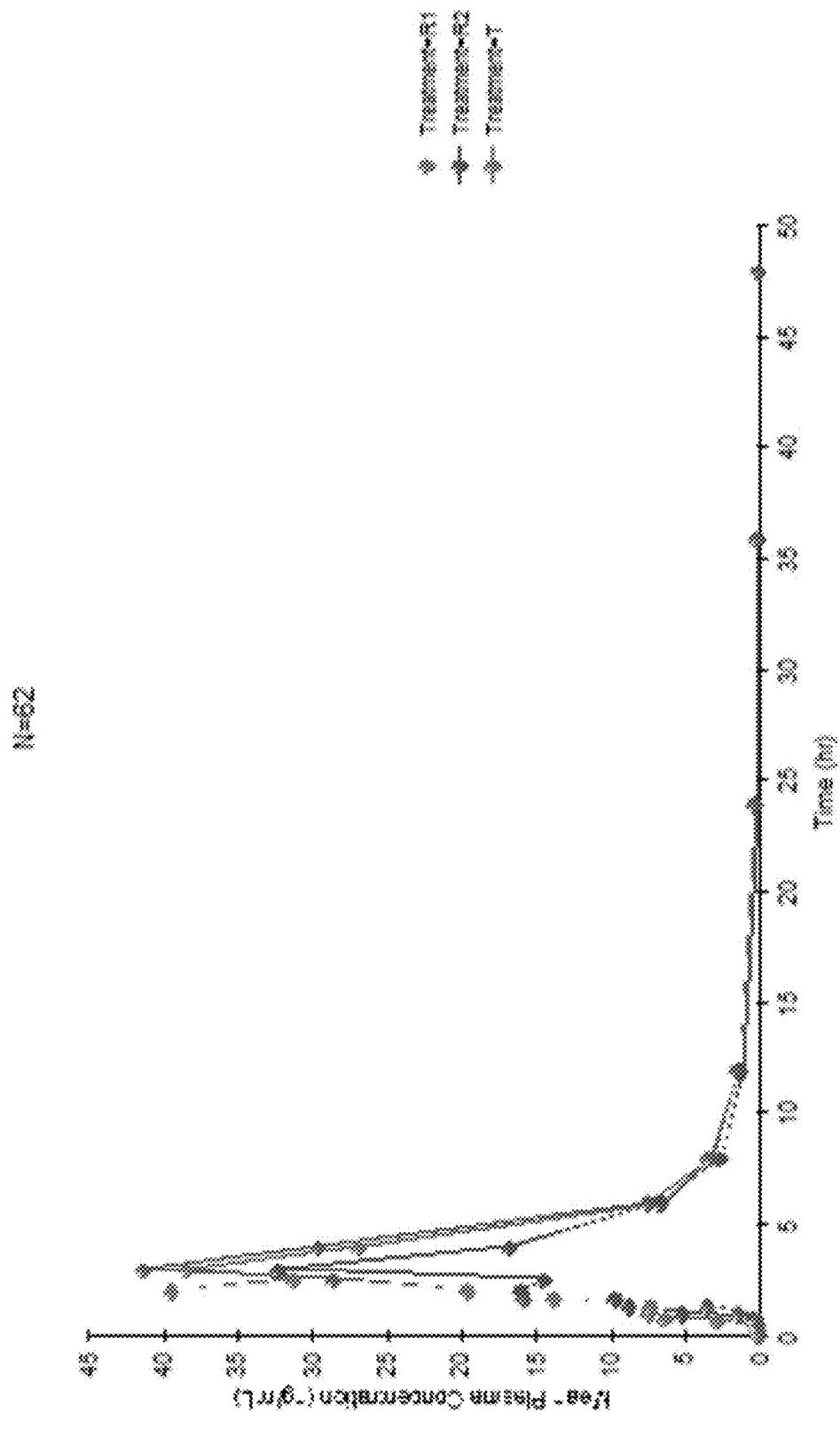
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Fig. 7: Linear Plot of Mean Plasma Progesterone (Corrected) Concentrations Versus Time (N=62)



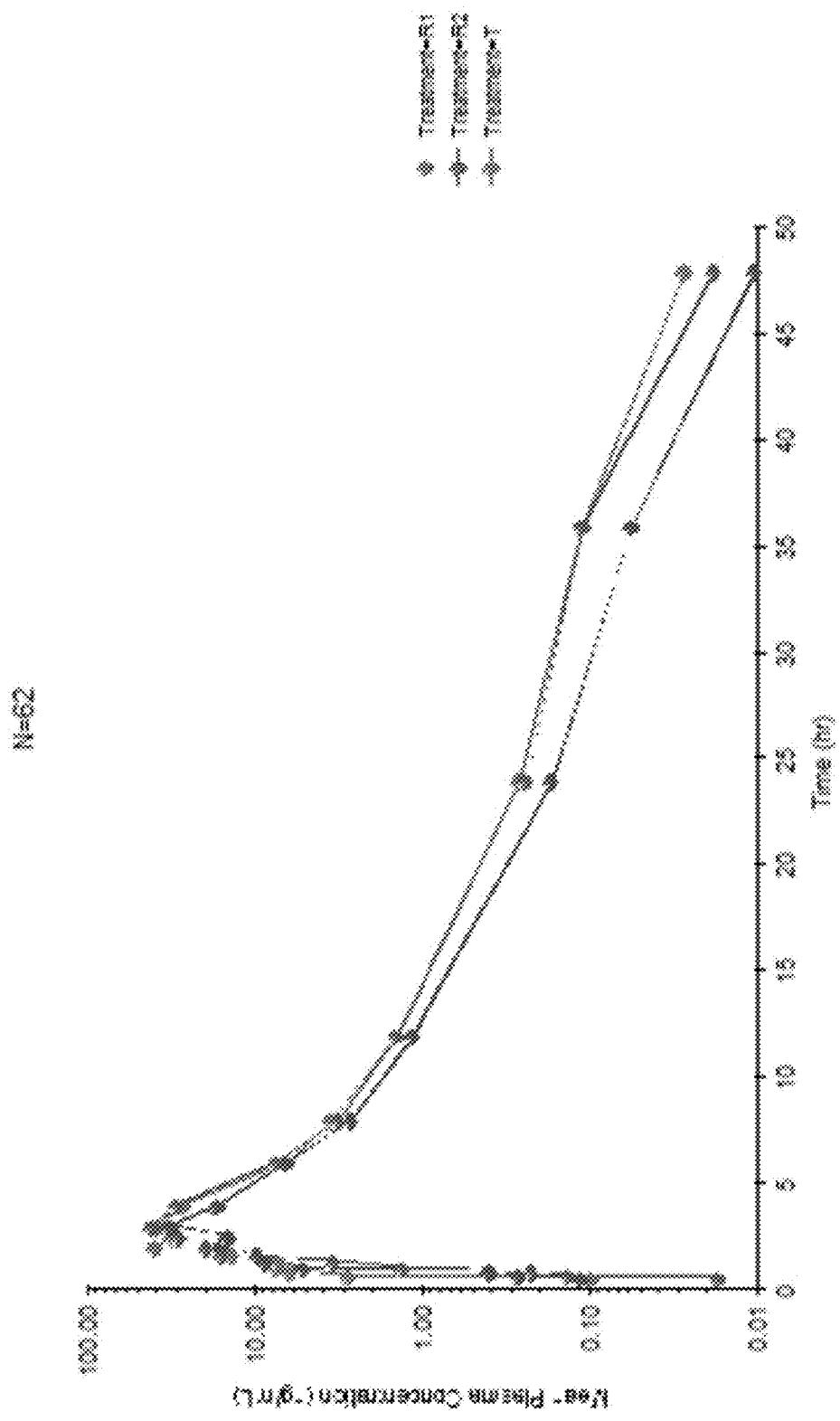
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Fig. 8—Semi-logarithmic Plot of Mean Plasma Progesterone (Corrected) Concentrations Versus Time (N=62)



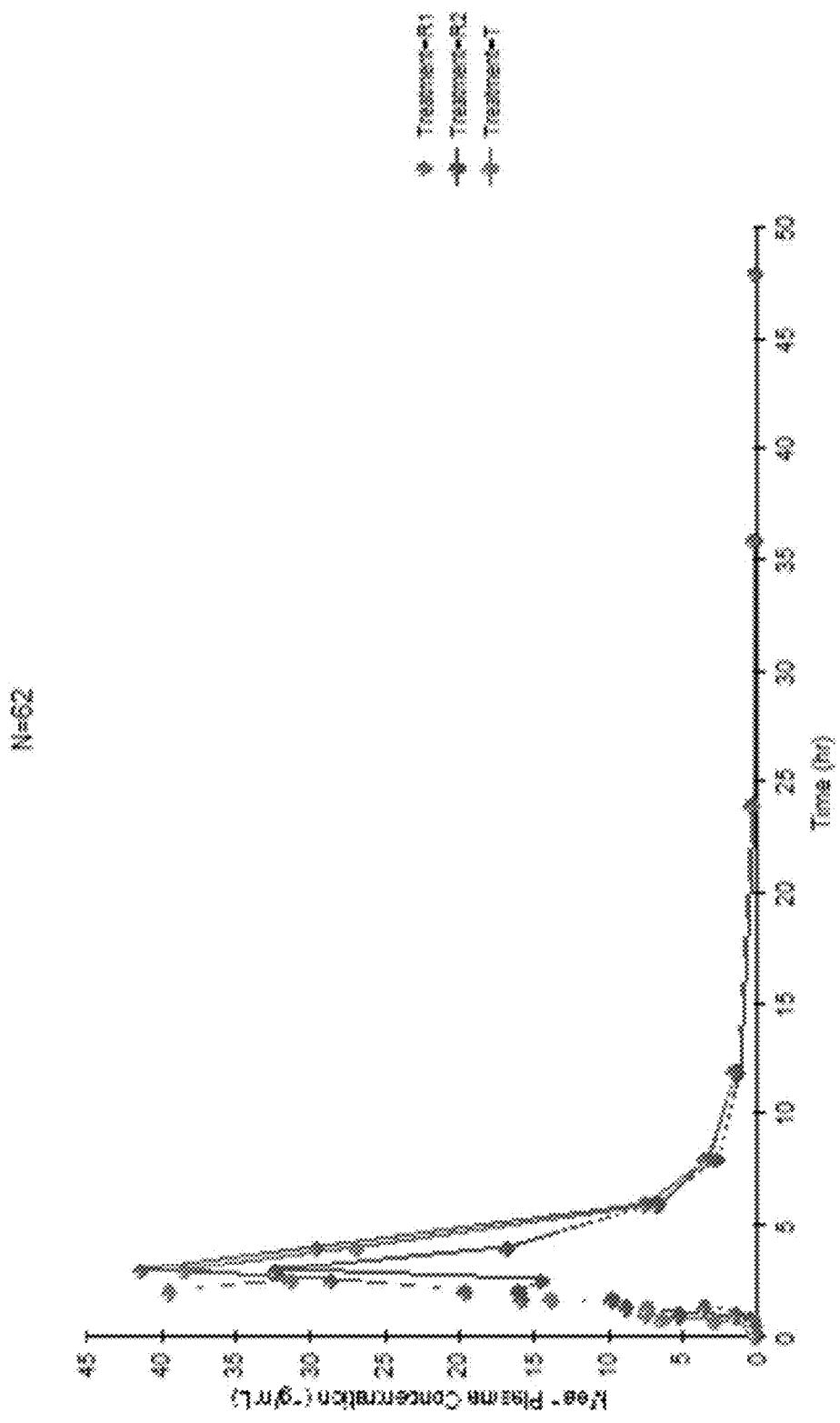
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Fig. 9 — Linear Plot of Mean Plasma Progesterone (Uncorrected) Concentrations Versus Time (N=62)



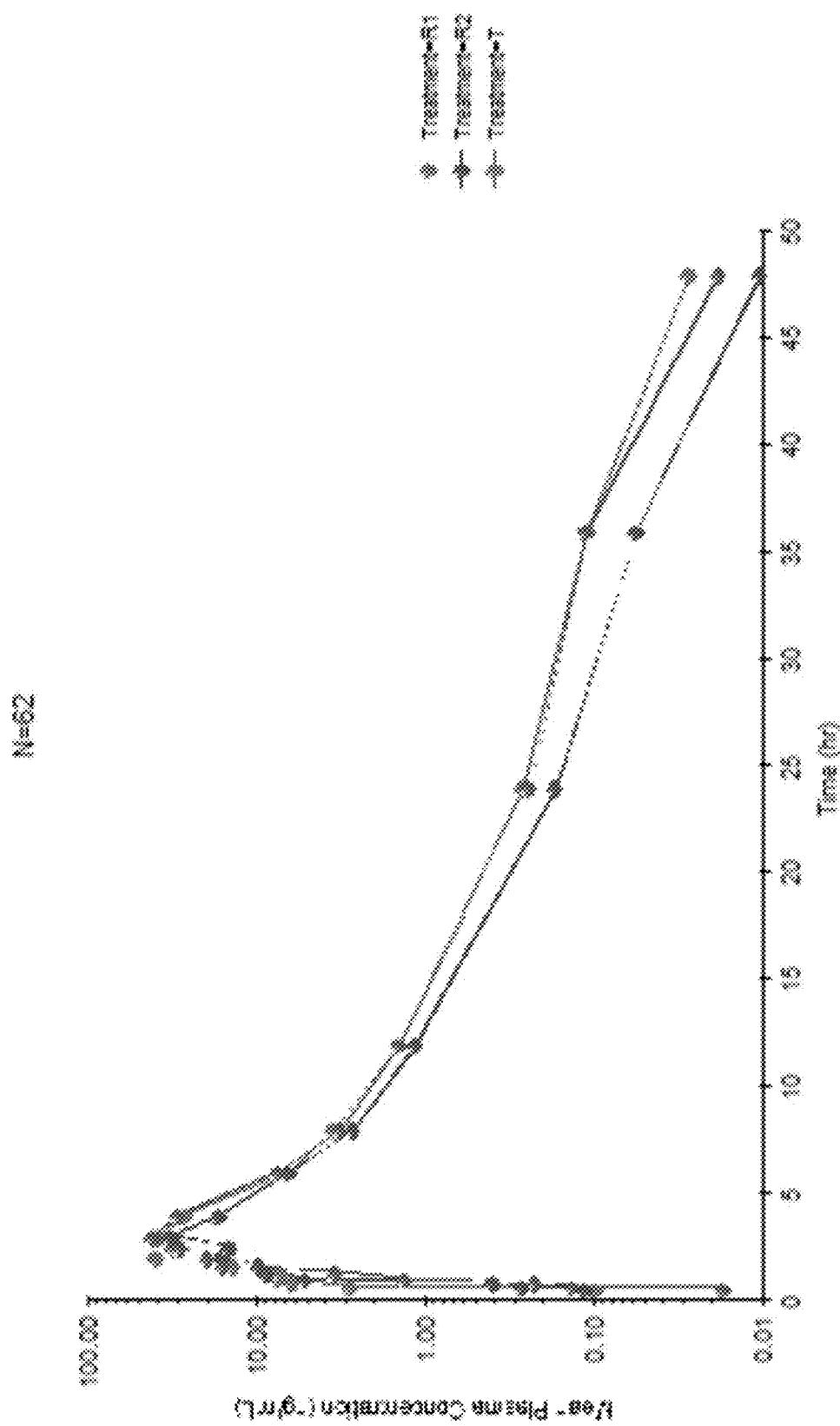
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Fig. 10—Semi-logarithmic Plot of Mean Plasma Progesterone (Uncorrected) Concentrations Versus Time (N=62)



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1**PROGESTERONE FORMULATIONS HAVING
A DESIRABLE PK PROFILE****CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application claims priority to U.S. Provisional Application 61/972,068 filed 28 Mar. 2014 and is a continuation in part of U.S. Ser. No. 14/125,547 filed 11 Dec. 2013 which is a National Stage application under 35 U.S.C. § 371 of International Application Serial No. PCT/US2013/046442, entitled "PROGESTERONE FORMULATIONS" which was filed on 18 Jun. 2013, and claims priority to the following U.S. Patent Applications: U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012; U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Nov. 21, 2012; U.S. Patent Application Serial No. PCT/US2013/023309, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Jan. 25, 2013; and U.S. patent application Ser. No. 13/843,362, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Mar. 15, 2013. This application also claims priority to U.S. patent application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013. Each of the aforementioned applications are incorporated herein by reference in their entirety.

FIELD OF INVENTION

This disclosure relates to progesterone formulations, methods of using these formulations, and their related pharmacokinetic parameters. Various progesterone formulations may be used in hormone therapies for menopausal, perimenopausal and post-menopausal females, for example, to mitigate side effects from estrogen replacement therapy. In addition, various progesterone formulations may be used to prevent preterm delivery in pregnant women having a shortened cervix. Progesterone can likewise be used to treat endometrial hyperplasia and amenorrhea.

BACKGROUND OF THE INVENTION

It is not uncommon for pre-menopausal, peri-menopausal, menopausal, or postmenopausal females, to experience vaginal dryness, vaginal odor, vulvar irritation and itching, dysuria (pain, burning or stinging when urinating), dysparenia (vaginal pain associated with sexual activity), or vaginal bleeding associated with sexual activity. They may also experience night sweats and menopausal hot flashes (vasomotor symptoms), soreness, increased or variant urinary frequency and urgency, urinary discomfort and incontinence ("estrogen-deficient urinary state(s)"), mood disturbances, and symptoms related vulvo-vaginal atrophy, endometrial hyperplasia, endometrial cancer, and other symptoms of estrogen-related disorders. These symptoms, and other symptoms known to those skilled in the art, are believed to be induced as a result of inadequate or irregular hormone production. As a result, prophylactic methods and treatment regimens to alleviate these symptoms frequently include low dosages of estrogens.

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But increased levels of estrogens, including estradiol, whether due to prescription or naturally-occurring increases, may lead to the symptoms and disorders previously mentioned. To mitigate the effect of increased estradiol levels on the endometrium, progesterone administration is often a prophylactic method or prescribed treatment to prevent the negative effects of estrogens such as endometrial hyperplasia and related disorders.

These prophylactic methods and prescribed treatments involving the use of one or more of a group of medications designed to supplement hormone levels in women who experience irregular or decreased hormone production or who lack adequate hormone production, may generally be referred to as hormone replacement therapy (HRT).

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to supplement hormone levels in women who lack adequate hormone production. It can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones.

HRT is available in various forms. One therapy involves administration of low dosages of one or more estrogen(s) or one or more chemical analogues. Another involves administration of progesterone or one or more chemical analogues. Among other effects, progesterone administration acts to mitigate certain undesirable side effects from estradiol administration or naturally-occurring elevated blood levels including endometrial hyperplasia (thickening) and prevention or inhibition of endometrial cancer. Progesterone is a C-21 steroid sex hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone is hydrophobic, having a reported aqueous solubility of 0.007 ± 0.0 mg/ml. Progesterone is poorly absorbed when administered orally.

Existing progesterone prophylactic methods and prescribed treatments inconsistently or irregularly achieve high levels of absorbed progesterone at low dosages of progesterone. Existing methods and treatments often use synthetic progestins. Synthetic progestins such as medroxyprogesterone acetate or norethindrone acetate have been specifically designed to resist enzymatic degradation and remain active after oral administration. However, these compounds exert undesirable effects on the liver (notably on lipids) and often cause psychological side effects that can be severe enough to contraindicate their use.

One conventional progesterone therapeutic is PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug, formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction. The active ingredient in PROMETRIUM is considered to be structurally identical to naturally occurring progesterone produced by a woman's body (also known as a "bioidentical").

Clinical trials involving PROMETRIUM have shown significant intra- and inter-patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean pharmacokinetic parameters listed in Table 1 (see Table 1, package insert for PROMETRIUM).

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TABLE 1

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C _{max} (ng/ml)	17.3 ± 21.9	38.1 ± 37.8	60.6 ± 72.5
T _{max} (hr)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC (0-10)(ng × hr/ml)	43.3 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

The unusually high variability in C_{max} and AUC, as evidenced by the large reported standard deviation, may indicate that a significant percentage of patients are over-dosed or receive a sub-optimal dose.

The presence of peanut oil in the formulation excludes patients who are allergic to peanut oil. Peanut oil, like other peanut products, may act as an allergen. Indeed, there is a portion of the population that has severe reactions to peanut oil. Peanut allergies are becoming a significant health concern. Food allergies are a leading cause of anaphylaxis, with approximately 200 deaths occurring annually in the United States. While incidence and prevalence are not entirely known, it is suspected that about 6% of children and 4% of adults in North America are affected by food allergies. Many food allergies experienced by children are generally outgrown in adulthood with the exception of peanut allergies.

Progesterone and its analogues can be used to treat a variety of medical conditions, including acute diseases or disorders, as well as chronic diseases and disorders associated with long-term declines of natural progesterone levels.

Accordingly, improved formulations of progesterone would be advantageous. To that end, and disclosed herein, are, among other things, a new softgel progesterone pharmaceutical composition containing solubilized or partially solubilized progesterone, suspended progesterone, a solubilizing agent, and a non-ionic surfactant.

SUMMARY OF THE INVENTION

Various pharmaceutical formulations are disclosed herein. For example, pharmaceutical formulations are disclosed comprising ultra-micronized progesterone. Moreover, pharmaceutical formulations are disclosed comprising formulations of ultra-micronized progesterone, wherein the ultra-micronized progesterone is combined with a suitable excipient.

Thus, in various illustrative embodiments, the invention comprises an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient. The progesterone can be fully solubilized, or, more typically, partially solubilized, in a solubilizing agent, with any insoluble progesterone being suspended in the solubilizing agent. The solubilizing agent can comprise a medium chain fatty acid-polyester or a mixture of medium chain fatty acid-polyol esters. The polyol can be, for example, a glycol such as ethylene glycol, polyethylene glycol, propylene glycol, polypropylene glycol, etc. In other embodiments, the polyol can be a triol such as glycerol. When the polyol is a glycol, the glycol can be mono- or di-esterified with a given fatty acid (simple) or can be a mixed di-ester using different medium chain fatty acids. When the polyol is glycerol, the glycerol can be mono-, di-, or tri-esterified giving a mono-glyceride, diglyceride, or triglyceride. Typical di- and tri-

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glycerides are simple triglycerides, though in certain embodiments, the di- and triglycerides can be mixed. In particular, embodiments, the solubilizing agent can comprise a simple, mixed, or combination simple and mixed glycol di-ester. In still other embodiments, the solubilizing agent can be a simple, mixed, or combination simple and mixed triglyceride. For example, in a particular embodiment, the solubilizing agent can comprise an oil having simple and mixed triglycerides prepared from predominantly C8 and C10 fatty acids. An example of such a triglyceride is MIGLYOL® 812.

In certain embodiments, the formulation can further comprise a non-ionic surfactant. As discussed elsewhere herein, the non-ionic surfactant can comprise GELUCIRE 44/14.

In certain embodiments the progesterone is micronized or ultra-micronized. In certain embodiments, at least about 80 wt % of the total progesterone is micronized. The fatty acids can be predominantly (>50 wt %): C6 to C12 fatty acids, C6 to C10 fatty acids, C8 to C12 fatty acids, or C8 to C10 fatty acids. Some embodiments comprise a non-ionic surfactant that comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol.

In other embodiments, a softgel progesterone pharmaceutical composition as a hormone replacement therapy (HRT), or as a prophylactic method or a prescribed treatment to mitigate the associated symptoms associated with irregular or inadequate hormone levels is provided.

In particular embodiments, this disclosure provides a pharmaceutical composition for orally administering progesterone to a subject in need thereof, the composition comprising: an amount of progesterone; a solubilizing agent; and a nonionic surfactant selected from the group consisting of lauroyl macrogol-32 glycerides EP (GELUCIRE 44/11), lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14), and caprylocaproyl macrogol-8 glycerides EP; wherein the solubilizing agent comprises at least one C6-C12 fatty acid mono-, di-, or tri-ester of glycerol and wherein the composition has a total mass.

In one embodiment, the solubilizing agent comprises at least one C6-C12 fatty acid mono-ester of glycerol.

In another embodiment, the solubilizing agent comprises at least one C6-C12 fatty acid di-ester of glycerol.

In another embodiment, the solubilizing agent comprises at least one C6-C12 fatty acid tri-ester of glycerol.

In yet another embodiment, the tri-ester of glycerol comprises predominantly esters of caprylic fatty acid (C8) and capric fatty acid (C₁₀).

In a further embodiment, the tri-ester of glycerol is MIGLYOL® 812.

In certain embodiments, the solubilizing agent is medium chain triglycerides (MIGLYOL® 812).

In certain embodiments, the nonionic surfactant is lauroyl polyoxyl-32 glycerides (GELUCIRE® 44/14).

In some embodiments, the amount of progesterone is from 25 mg to 200 mg.

In particular embodiments, the amount of progesterone is 75 mg or 150 mg.

In some embodiments, the amount of progesterone includes a solubilized amount of progesterone and a suspended amount of progesterone.

In certain embodiments, the composition is provided in a gelatin capsule.

In some embodiments, the total mass of the composition is less than 500 mg.

In other embodiments, the composition provides increased progesterone bioavailability compared to micronized progesterone suspended in peanut oil.

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In certain embodiments, the solubilizing agent comprises predominantly at least one C6-C12 fatty acid mono-, di-, or tri-ester of glycerol.

In other embodiments, this disclosure provides a pharmaceutical composition for orally administering progesterone to a subject in need thereof, the composition comprising: 75, 150, 200, or 300 mg of progesterone; a solubilizing agent comprising predominantly a triglyceride oil of C8 and C10 fatty acid esters; and lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14).

This disclosure also provides a method of preventing endometrial hyperplasia, the method comprising administering to a patient in need thereof a composition comprising: an amount of progesterone; a solubilizing agent; and a nonionic surfactant selected from the group consisting of lauroyl macrogol-32 glycerides EP (GELUCIRE 44/11), lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14), and caprylocaproyl macrogol-8 glycerides EP; wherein the solubilizing agent comprises at least one C6-C12 fatty acid mono-, di-, or tri-ester of glycerol and wherein the composition has a total mass.

In certain embodiments of the method, the amount of progesterone is 150 mg.

In other embodiments, this disclosure provides a method of treating amenorrhea, the method comprising administering to a patient in need thereof a composition comprising: an amount of progesterone; a solubilizing agent; and a nonionic surfactant selected from the group consisting of lauroyl macrogol-32 glycerides EP (GELUCIRE 44/11), lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14), and caprylocaproyl macrogol-8 glycerides EP; wherein the solubilizing agent comprises at least one C6-C12 fatty acid mono-, di-, or tri-ester of glycerol and wherein the composition has a total mass.

In certain embodiments of the noted method, the amount of progesterone is 150 mg or 300 mg.

In certain embodiments, the amount of progesterone comprises about 33% by weight of the composition; the solubilizing agent comprises about 65% by weight of the composition, the non-ionic surfactant comprises about 1.7% by weight of the composition.

In further embodiments, the amount of progesterone comprises about 33.33% by weight of the composition; the solubilizing agent comprises about 64.93% by weight of the composition, the non-ionic surfactant comprises about 1.67% by weight of the composition.

In certain embodiments, the composition further comprises an antioxidant.

In particular embodiments, the antioxidant is butylated hydroxy toluene.

In certain embodiments, the solubilizing agent is MIGLYOL 812.

In certain embodiments, the non-ionic surfactant is lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14).

In some embodiments, the amount of progesterone is 200 mg.

In other embodiments, the amount of progesterone is 150 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate embodiments of the disclosure, and together with the description serve to explain the principles of the disclosure.

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FIG. 1 illustrates a process to produce fill material in accordance with various embodiments;

FIG. 2 illustrates a process to produce softgel capsules in accordance with various embodiments;

FIG. 3 illustrates a process to produce softgel capsules in accordance with various embodiments; and

FIG. 4 illustrates a dissolution study of a formulation in accordance with various embodiments.

FIG. 5 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 6 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

FIG. 7 illustrates a Linear Plot of Mean Plasma Progesterone (Corrected) Concentrations Versus Time (N=62).

FIG. 8 illustrates a graph that is a Semi-logarithmic Plot of Mean Plasma Progesterone (Corrected) Concentrations Versus Time (N=62).

FIG. 9 illustrates a graph that is a Linear Plot of Mean Plasma Progesterone (Uncorrected) Concentrations Versus Time (N=62).

FIG. 10 illustrates a graph that is a Semi-logarithmic Plot of Mean Plasma Progesterone (Uncorrected) Concentrations Versus Time (N=62).

DETAILED DESCRIPTION

This disclosure provides a pharmaceutical formulation comprising progesterone and a solubilizing agent. In some embodiments, a pharmaceutical formulation comprising ultra-micronized progesterone is provided. As described in detail herein, various solubilizing agents, lubricants, and other excipients may be included. In further embodiments, ultra-micronized progesterone formulations provide improved bioavailability and other pharmacokinetic improvements. These embodiments are described in sufficient detail to enable those skilled in the art to practice these embodiments. Further, other embodiments may be used and other changes may be made without departing from the scope of this disclosure. The following detailed description is therefore not to be taken in a limiting sense. As used in this disclosure, the term "or" is a logical disjunction and does not indicate an exclusive disjunction unless expressly indicated as such with the terms "either," "unless," "alternatively," and words of similar effect.

Definitions

Unless otherwise specified, the following definitions apply.

The phrase "active pharmaceutical ingredient" or "API" as used herein, means the active compound(s) used in formulating a drug product. In exemplary embodiments, the API is progesterone.

The term "bioequivalent" has the meaning prescribed in 21 CFR § 320.1(e), e.g. the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes

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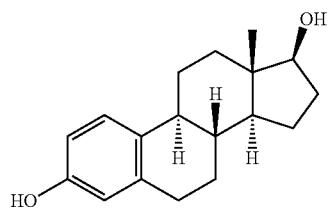
available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. In practice, two products are considered bioequivalent if the 90% confidence interval of the C_{max} , AUC, or, optionally, T_{max} is within 80.00% to 125.00%.

The term "bioidentical" or "natural" used in conjunction with the hormones disclosed herein, means hormones that are identical to or match the chemical structure and effect of those that occur naturally or endogenously in the human body. An exemplary natural estrogen is estradiol.

The term "drug product" as used herein means at least one API in combination with at least one excipient, wherein the API and at least one excipient are provided in unit dosage form.

The term "estrogen" means generally the different hormone types of estrogen, synthetically or naturally occurring, including estradiol, estriol, and estrone.

The term "estradiol" means (17β) -estr-1,3,5(10)-triene-3,17-diol. Estradiol is also called 17β -estradiol, oestradiol, or E2 and is found endogenously in the human body. Irrespective of the what it is called, estradiol refers to the bio-identical form of estradiol found in the human body having the structure:



Estradiol is supplied in an anhydrous or a hemi-hydrate form; for the purposes of this disclosure, the anhydrous form or the hemihydrate form can be substituted for the other by accounting for the water or lack of water according to well-known and understood techniques.

The phrase "equivalent dosage form" as used herein refers to a dosage form that is identical to a reference dosage form in composition (e.g. identical solubilizing agent(s), non-ionic surfactant(s), and API), but differs from the reference dosage form in the amount of API present or in the ratio of the various components in the reference dosage form.

The term "ultra-micronized progesterone," as used herein, refers to micronized progesterone having an X50 particle size value below about 20 microns or having an X90 value below about 25 microns. The term "X50" as used herein, means that half of the particles in a sample are smaller in diameter than a given number. For example, ultra-micronized progesterone having an X50 of 5 microns means that, for a given sample of ultra-micronized progesterone, half of the particles have a diameter of less than 5 microns. In that regard, similar terms, in the form XYY mean that YY percent of the particles in the sample are smaller in diameter than a given number. For example, X90 means that ninety percent of the particles in a sample are smaller in diameter than a given number.

The term "administer," "administration," "deliver" or "delivery" (collectively "administration"), as used herein, means oral administration of the formulation disclosed herein, preferably in a soft gelatin capsule.

The term "glyceride" is an ester of glycerol (1,2,3-propanetriol) with acyl radicals of fatty acids and is also

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known as an acylglycerol. If only one position of the glycerol molecule is esterified with a fatty acid, a "monoglyceride" is produced; if two positions are esterified, a "diglyceride" is produced; and if all three positions of the glycerol are esterified with fatty acids, a "triglyceride" or "triacylglycerol" is produced. A glyceride is "simple" if all esterified positions contain the same fatty acid; whereas a glyceride is "mixed" if the esterified positions contained different fatty acids. The carbons of the glycerol backbone are designated sn-1, sn-2 and sn-3, with sn-2 being in the middle carbon and sn-1 and sn-3 being the end carbons of the glycerol backbone.

The term "medium chain" is used to describe the aliphatic chain length of fatty acid containing molecules. "Medium chain" specifically refers to fatty acids, fatty acid esters, or fatty acid derivatives that contain fatty acid aliphatic tails or carbon chains that contain 6 (C6) to 14 (C14) carbon atoms, 8 (C8) to 12 (C12) carbon atoms, or 8 (C8) to 10 (C10) carbon atoms.

The terms "medium chain fatty acid" and "medium chain fatty acid derivative" are used to describe fatty acids or fatty acid derivatives with aliphatic tails (i.e., carbon chains) having 6 to 14 carbon atoms. Fatty acids consist of an unbranched or branched aliphatic tail attached to a carboxylic acid functional group. Fatty acid derivatives include, for example, fatty acid esters and fatty acid containing molecules, including, without limitation, mono-, di- and triglycerides that include components derived from fatty acids.

Fatty acid derivatives also include fatty acid esters of ethylene or propylene glycol. The aliphatic tails can be saturated or unsaturated (one or more double bonds between carbon atoms). In some embodiments, the aliphatic tails are saturated (i.e., no double bonds between carbon atoms). Medium chain fatty acids or medium chain fatty acid derivatives include those with aliphatic tails having 6-14 carbons, including those that are C6-C14, C6-C12, C8-C14, C8-C12, C6-C10, C8-C10, or others. Examples of medium chain fatty acids include, without limitation, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, and derivatives thereof.

The term "oil," as used herein, refers to any pharmaceutically acceptable oil, especially medium chain oils, and specifically excluding peanut oil, that can suspend and/or solubilize bioidentical progesterone and/or estradiol, including starting materials and/or precursors thereof, including micronized progesterone and/or micronized estradiol as described herein.

The term "medium chain oil" refers to an oil wherein the composition of the fatty acid fraction of the oil is predominantly medium chain (i.e., C6 to C14) fatty acids, i.e., the composition profile of fatty acids in the oil is predominantly medium chain. As used herein, "predominantly" means that between 20% and 100% (inclusive of the upper and lower limits) of the fatty acid fraction of the oil is made up of medium chain fatty acids, i.e., fatty acids with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. In some embodiments, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 85%, about 90% or about 95% of the fatty acid fraction of the oil is made up of medium chain fatty acids. Those of skill in the art that will readily appreciate that the terms "alkyl content" or "alkyl distribution" of an oil can be used in place of the term "fatty acid fraction" of an oil in characterizing a given oil or solubilizing agent, and these terms are used interchangeable herein. As such, medium chain oils suitable for use in the formulations disclosed herein include medium chain oils

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wherein the fatty acid fraction of the oil is predominantly medium chain fatty acids, or medium chain oils wherein the alkyl content or alkyl distribution of the oil is substantially medium chain alkyls (C6-C12 alkyls). It will be understood by those of skill in the art that the medium chain oils suitable for use in the formulations disclosed herein are pharmaceutical grade (e.g., pharmaceutical grade medium chain oils). Examples of medium chain oils include, for example and without limitation, medium chain fatty acids, medium chain fatty acid esters of glycerol (e.g., for example, mono-, di-, and triglycerides), medium chain fatty acid derivatives of propylene glycol, medium chain fatty acid derivatives of polyethylene glycol, and combinations thereof.

The term "ECN" or "equivalent carbon number" means the sum of the number of carbon atoms in the fatty acid chains of an oil, and can be used to characterize an oil as, for example, a medium chain oil or a long-chain oil. For example, tripalmitin (tripalmitic glycerol), which is a simple triglyceride containing three fatty acid chains of 16 carbon atoms, has an ECN of $3 \times 16 = 48$. Conversely, a triglyceride with an ECN=40 may have "mixed" fatty acid chain lengths of 8, 16 and 16; 10, 14 and 16; 8, 14 and 18; etc. Naturally occurring oils are frequently "mixed" with respect to specific fatty acids, but tend not to contain both long chain fatty acids and medium chain fatty acids in the same glycerol backbone. Thus, triglycerides with ECN's of 21-42 typically contain predominately medium chain fatty acids; while triglycerides with ECN's of greater than 43 typically contain predominately long chain fatty acids. For example, the ECN of corn oil triglyceride in the USP would be in the range of 51-54. Medium chain diglycerides with ECN's of 12-28 will often contain predominately medium chain fatty chains, while diglycerides with ECN's of 32 or greater will typically contain predominately long chain fatty acid tails. Monoglycerides will have an ECN that matches the chain length of its sole fatty acid chain. Thus, monoglyceride ECN's in the range of 6-14 contain mainly medium chain fatty acids, and monoglycerides with ECN's 16 or greater will contain mainly long chain fatty acids.

The average ECN of a medium chain triglyceride oil is typically 21-42. For example, as listed in the US Pharmacopeia (USP), medium chain triglycerides having the following composition as the exemplary oil in the table below

Fatty-acid Tail Length	% of oil	Exemplary Oil
6	≤2.0	2.0
8	50.0-80.0	70.0
10	20.0-50.0	25.0
12	≤3.0	2.0
14	≤1.0	1.0

would have an average ECN of $3 * [(6 * 0.02) + (8 * 0.70) + (10 * 0.25) + (12 * 0.02) + (14 * 0.01)] = 25.8$. The ECN of the exemplary medium chain triglycerides oil can also be expressed as a range (per the ranges set forth in the USP) of 24.9-27.0. For oils that have mixed mono-, di-, and triglycerides, or single and double fatty acid glycols, the ECN of the entire oil can be determined by calculating the ECN of each individual component (e.g., C8 monoglycerics, C8 diglycerides, C10 monoglycerides, and C10 monoglycerides) and taking the sum of the relative percentage of the component multiplied by the ECN normalized to a monoglyceride for each component. For example, the oil having C8 and C10 mono- and diglycerides shown in the table below has an ECN of 8.3, and is thus a medium chain oil.

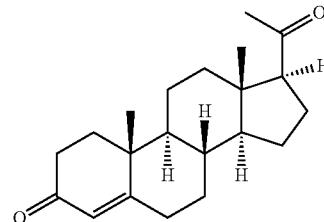
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Fatty-acid Tail Length	% of oil	ECN as % of oil (chain length) × (% in oil)	ECN as % of oil normalized to monoglyceride
C8 monoglyceride	47	$8 \times 0.47 = 3.76$	3.76
C10 monoglyceride	8	$10 \times 0.08 = 0.8$	0.8
C8 diglyceride	38	$2 \times (8 \times 0.38) = 6.08$	$6.08/2 = 3.04$
C10 diglyceride	7	$2 \times (10 \times 0.07) = 1.4$	$1.4/2 = 0.7$
OIL ECN (normalized to monoglycerides)			8.3

Expressed differently, ECN can be calculated as each chain length in the composition multiplied by its relative percentage in the oil: $(8 * 0.85) + (10 * 0.15) = 8.3$.

The term "patient" refers to a human individual who has received, who might receive, or is receiving health or pharmaceutical care, or is under the supervision and care of a physician, pharmacist, or medically trained professional. This individual may be expecting this care, may be currently receiving it, or may have already received it.

The term "progesterone" refers to pregn-4-ene-3,20-dione. Progesterone is also interchangeably called P4 and is found endogenously in the human body. As used herein, progesterone refers to the bio-identical or body-identical form of progesterone found in the human body having the structure:



The term "solubilized progesterone" means that the progesterone or a portion thereof is solubilized or dissolved in the solubilizing agent(s) or the formulations disclosed herein. In some embodiments, the progesterone is "partially solubilized" with a portion of the progesterone being solubilized or dissolved in the solubilizing agent and a portion of the progesterone being suspended in the solubilizing agent. Partially solubilized progesterone may include progesterone that is about 1% solubilized, about 5% solubilized, about 10% solubilized, about 15% solubilized, or about 20% solubilized, about 30% solubilized, about 40% solubilized, about 50% solubilized, about 60% solubilized, about 70% solubilized, about 80% solubilized, about 85% solubilized, about 90% solubilized or about 95% solubilized. In other embodiments, the progesterone is "fully solubilized" with all or substantially all of the progesterone being solubilized or dissolved in the solubilizing agent. Fully solubilized progesterone may include progesterone that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. In particular embodiments, the progesterone is less than about 20% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The term "pharmaceutical composition" refers to a composition comprising at least a solubilizing agent and progesterone. As used herein, pharmaceutical compositions are delivered, for example via oral administration. Furthermore,

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as used herein, "pharmaceutical composition" and "formulation" are used interchangeably.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in gastric juices compared to PROMETRIUM.

The term "gastric juices" means the watery, acidic digestive fluid that is secreted by various glands in the mucous membrane of the stomach and consists chiefly of hydrochloric acid, pepsin, rennin, and mucin.

The term "excipients," as used herein, refers to non-API substances such as solubilizing agents, anti-oxidants, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "carrier," as used herein, means any substance or mixture of substances that may be mixed with or contain an API (e.g., ultra-micronized progesterone). The term carrier is interchangeable with solubilizing agent.

The term "capsule," as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products, and includes hard or soft shell capsules.

The term "softgel," includes soft shell capsules, including soft-gelatin capsules and soft vegetable-based capsules, and soft capsules made from other materials providing the composition of such soft capsules are compatible with the formulations of the various embodiments described herein. A softgel may comprise two primary phases: a gel or vegetable-based capsule and a fill material of the pharmaceutical formulation as described herein. In particular embodiments, the weight of the fill material does not exceed 500 mg, i.e. the fill material weighs less than 500 mg, less than 450 mg, less than 400 mg, less than 350 mg, less than 300 mg, less than 250 mg, less than 200 mg, or less than 150 mg.

The term "bioavailability" has the meaning prescribed in 21 CFR § 320.1(a): the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action. For example, bioavailability can be measured as the amount of API in the blood (serum or plasma) as a function of time. Pharmacokinetic (PK) indicators such as AUC, C_{max} , or T_{max} may be used to measure and assess bioavailability. Absorption as used in this definition can include absorption in the stomach, intestines, or other tissue that help facilitate absorption of the API into the bloodstream.

The term "co-administered" as used herein, means that two drug products are administered simultaneously or sequentially on the same or different days.

The terms "pharmacokinetics," "pharmacokinetic measurements," "pharmacokinetic parameters," and "PK parameters" refers to parameters or measures used to assess bioavailability such as AUC, C_{max} , or T_{max} include assessments and determinations to study absorption, distribution, metabolism, and excretion of a drug.

The term "reference listed drug product" ("RLD") means PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug,

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formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction.

The term "secretory activity" refers to complete and partial secretory activity of the endometrium as is well understood in the art and as is discussed at length in Noyes, R. W., Hertig, A. T. and Rock, J. (1950), Dating the endometrial biopsy. Fertil. Steril., 1, 3-25, which is incorporated herein by reference. See also, Deliquisch, L., (1993), Effects of hormone therapy on the endometrium. Mod Pathol. January, vol. 6(1), pp 94-106, which is incorporated herein by reference. Noyes et al., is also referenced for additional information regarding endometrial biopsies.

The term "solubilized" refers to the amount of an API that is in solution. Solubility and percent solubility are expressed herein as a mass fraction (mg/g) or (% w/w, also referred to as wt. %).

The term "solubilizing agent" refers to an agent or combination of agents that solubilize an active pharmaceutical ingredient (e.g., estradiol or progesterone). For example and without limitation, suitable solubilizing agents include medium chain oils and other solvents and co-solvents that solubilize or dissolve an active pharmaceutical ingredient to a desirable extent. Solubilizing agents suitable for use in the formulations disclosed herein are pharmaceutical grade solubilizing agents (e.g., pharmaceutical grade medium chain oils). It will be understood by those of skill in the art that other excipients or components can be added to or mixed with the solubilizing agent to enhance the properties or performance of the solubilizing agent or resulting formulation. Examples of such excipients include, but are not limited to, surfactants, emulsifiers, thickeners, colorants, flavoring agents, etc. In some embodiments, the solubilizing agent is a medium chain oil and, in some other embodiments, the medium chain oil is combined with a co-solvent(s) or other excipient(s).

The term "subject" refers to both human and non-human animal subjects who are administered the pharmaceutical composition of this disclosure. Specifically intended are mammalian subjects. More specifically intended are human subjects.

The term "area under the curve" or "AUC" refers to the area under the curve defined by changes in the blood concentration of an active pharmaceutical ingredient (e.g., progesterone), or a metabolite of the active pharmaceutical ingredient, over time following the administration of a dose of the active pharmaceutical ingredient. " $AUC_{0-\infty}$ " is the area under the concentration-time curve extrapolated to infinity following the administration of a dose. " AUC_{0-t} " is the area under the concentration-time curve from time zero to time t following the administration of a dose, wherein t is the last time point with a measurable concentration.

The term " C_{max} " refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of an active pharmaceutical ingredient (e.g., progesterone), or a metabolite of the active pharmaceutical ingredient, over time.

The term " T_{max} " refers to the time that it takes for the blood concentration of an active pharmaceutical ingredient (e.g., estradiol or progesterone), or a metabolite of the active pharmaceutical ingredient, to reach the maximum value.

Optionally, the term, " $T_{1/2}$ " as used herein, refers to the time that it takes for progesterone blood concentration to decline to one-half of the maximum level.

Collectively AUC, C_{max} , and optionally T_{max} and $T_{1/2}$, are the principle pharmacokinetic parameters that can charac-

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terize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

DESCRIPTION

Provided herein are oral pharmaceutical compositions comprising solubilized or partially solubilized progesterone. Further disclosed herein are data demonstrating the efficacy of these pharmaceutical compositions, as well as methods of using the described pharmaceutical compositions. Generally, the pharmaceutical compositions disclosed herein can be useful in mitigating the symptoms and effects of increased, decreased, or irregular estrogen levels.

Additional aspects and embodiments of this disclosure include: providing increased patient ease of use while potentially minimizing certain side effects from erroneous use, providing reduced metabolic and vascular side effects of commonly used synthetic progesterone, providing reduced food and allergy effects, providing improved bioavailability of progesterone as compared to the PROMETRIUM®, and in some embodiments providing for improved bioavailability of progesterone or a bioequivalent progesterone product at a reduced dose of API compared to the RLDs.

Various embodiments are improvements over existing progesterone formulations, treatments, and methods of using these formulations and treatments. While not bound by theory, the elements of the pharmaceutical compositions of this disclosure provide improved bioavailability, improved pharmacokinetics, bioequivalent pharmaceutical compositions, and the potential to reduce the administered dosage strength. Bioavailability comparisons to commercially available forms, such as tablet and capsule forms, may be determined by standard pharmacokinetic techniques.

In embodiments, progesterone is solubilized or partially solubilized (partially suspended) when administered. The type of progesterone used, the form of that progesterone (i.e., solubilized or suspended), the different solubilizing agent used, the different excipients used, and the administration under proper conditions (i.e. fed, absence of concomitant medications, etc.) contribute, in part, to the improvements over existing progesterone compositions, methods, and treatments.

In embodiments, the pharmaceutical compositions do not include peanut oil.

In certain embodiments, the API is progesterone, which is solubilized or partially solubilized (partially suspended). In embodiments, progesterone is the sole API.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules or softgels of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Ultra-micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

In illustrative embodiments, total progesterone, i.e., dissolved and suspended progesterone, can be 20 to 50 wt %, e.g., 30 to 35 wt %, based on the weight of the entire fill, i.e., the liquid pharmaceutical formulation.

Other embodiments disclosed herein further provide more uniform dissolution of progesterone and reduced intra- and inter-patient PK parameters when compared to equal dosages of PROMETRIUM. Dissolution uniformity of progesterone in a formulation of this disclosure compared to PROMETRIUM at equal dosage strengths and using the same USP apparatus can be determined using standard

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techniques established for API dissolution testing, including that which is described in the examples below.

According to the PROMETRIUM prescribing information, progesterone absorption is highly variable from patient to patient and within the same patient. A clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C _{max} (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
T _{max} (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC ₀₋₁₀ (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

These values are highly variable as demonstrated by their standard deviations which, in some cases, exceed 100% of the noted mean value. In particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

Reduced intra- and inter-patient variability of progesterone according to this disclosure compared to PROMETRIUM can be assessed using techniques known to those of ordinary skill in the art and described elsewhere herein.

Other aspects of this disclosure include the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States") in a subject in need of treatment, and with a non-toxic effective amount of said formulations.

The terms "treat," "treating," and "treatment" refer to any indicia of success in the treatment or amelioration of an injury, disease, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, disease, or condition more tolerable to the patient; slowing in the rate of degeneration or decline; or improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subject parameters, including the results of a physical examination, neuropsychiatric examinations, or psychiatric evaluation.

For purposes of this disclosure, "prophylaxis" refers to administration of the progesterone, to an animal, especially a mammal, and in particular a human, to protect the animal from any of the disorders set forth herein, as well as others, before or after the disorder has occurred in the subject.

Exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. In embodiments, progesterone dosage strength is from at least 25 mg to at least 200 mg. Specific dosage embodiments contain at least: 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg,

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79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 110 mg, 111 mg, 112 mg, 113 mg, 114 mg, 115 mg, 116 mg, 117 mg, 118 mg, 119 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, 140 mg, 141 mg, 142 mg, 143 mg, 144 mg, 145 mg, 146 mg, 147 mg, 148 mg, 149 mg, 150 mg, 151 mg, 152 mg, 153 mg, 154 mg, 155 mg, 156 mg, 157 mg, 158 mg, 159 mg, 160 mg, 161 mg, 162 mg, 163 mg, 164 mg, 165 mg, 166 mg, 167 mg, 168 mg, 169 mg, 170 mg, 171 mg, 172 mg, 173 mg, 174 mg, 175 mg, 176 mg, 177 mg, 178 mg, 179 mg, 180 mg, 181 mg, 182 mg, 183 mg, 184 mg, 185 mg, 186 mg, 187 mg, 188 mg, 189 mg, 190 mg, 191 mg, 192 mg, 193 mg, 194 mg, 195 mg, 196 mg, 197 mg, 198 mg, 199 mg, or 200 mg of progesterone per capsule.

In certain embodiments, the pharmaceutical compositions can contain at least about 50 mg, 75 mg, 100 mg, 150 mg, or 200 mg of progesterone. In certain embodiments, the pharmaceutical compositions contain from about 25 mg to about 50 mg, from about 75 mg to 100 mg, from about 50 mg to about 100 mg, about 75 mg, about 150 mg, about 200 mg, from about 100 mg to 150 mg, from about 150 mg to 200 mg, from 100 mg to 200 mg of progesterone. The lowest clinically effective dose of progesterone is used for treatment symptoms occurring due to irregular or inadequate hormone production, or for estrogen HRT patients. In one embodiment, the progesterone dosage is about 75 mg. In another embodiment, the progesterone dosage is about 150 mg. In another embodiment, the progesterone dosage is about 200 mg. In particular embodiments, the dosage is 75 mg, 150 mg, or 200 mg.

Solubilized compositions of this disclosure can be formulated for administration using techniques disclosed herein, and also using techniques well known in the art. Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises progesterone, at least 75% of the progesterone being solubilized (the balance being suspended/ultra-micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and di-esters of one or more glycols, with or without surfactant.

In other embodiments, the progesterone in the pharmaceutical compositions is not more than about 20% solubilized, not more than about 19% solubilized, not more than about 18% solubilized, not more than about 17% solubilized, not more than about 16% solubilized, not more than about 15% solubilized, not more than about 14% solubilized, not more than about 13% solubilized, not more than about 12% solubilized, not more than about 11% solubilized, not more than about 10% solubilized, not more than about 9% solubilized, not more than about 8% solubilized, not more than about 7% solubilized, not more than about 6% solubilized, or not more than about 5% solubilized, with the balance being suspended in the formulation as discussed elsewhere herein. The suspended/ultra-micronized progesterone is absorbable by the body and retains biological functionality despite not being soluble in the formulation. In a particular embodiment, the progesterone is about 15% solubilized in the formulation, with balance (about 85%) being suspended/ultra-micronized. In another embodiment, the progesterone is about 5% solubilized in the formulation, with balance (about 95%) being suspended/ultra-micronized.

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In certain embodiments, progesterone solubility in various solubilizing agents ranges from 27 mg/g to 95 mg/g. More specifically, in certain embodiments, progesterone's solubility in solubilizing agents is from 27.8 mg/g, 57.4 mg/g, 70.5 mg/g, 73.4 mg/g, 86.4 mg/g, to 95 mg/g.

Progesterone may be micronized/ultra-micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan.

Particle size may be determined in any suitable manner. 10 For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. Particle size may be represented by various metrics, for example, through an X50 particle size, or X90 particle size, or similar descriptions of 15 particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the 20 size range of 0.017 μm to 2000 μm . The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used 25 may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and 30 a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, or 1,4-dioxane. The Beck- 35 man Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software 40 may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various 45 embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of 50 suspending samples in the size range of 0.4 μm to 2000 μm . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous 55 and non-aqueous.

In various embodiments, ultra-micronized progesterone has an X50 value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns; and an X90 value of less than about 25 microns, less than about 20 microns, or less than about 15 microns.

In various embodiments, ultra-micronized progesterone is formulated with peanut and peanut-oil free excipients.

Solvent System

60 In various embodiments, a solvent system solubilizes one or more APIs, and in particular, progesterone. The solvent system is a mixture of solubilizing agents, together with

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co-solvents, surfactants, or other excipients. In certain embodiments, the solvent system comprises non-toxic, pharmaceutically acceptable solvents (alternatively referred to as "carriers"), co-solvents, surfactants, and excipients suitable for oral administration or absorption.

In embodiments, oils having medium chain fatty acids as a predominant or majority component are used as solubilizing agents/carriers to solubilize the one or more APIs. In certain embodiments, the solubilizing agents comprise medium chain fatty acid esters (e.g., esters of glycerol, ethylene glycol, or propylene glycol) or mixtures thereof. In certain embodiments, the medium chain fatty acids comprise chain lengths from C6 to C14. In certain embodiments the medium chain fatty acids comprise chain lengths from C6 to C12. In still other embodiments, the medium chain fatty acids are mono-, di-, or triglycerides predominately with chain lengths from C8 to C10. As noted elsewhere herein, the medium chain fatty acids can be saturated. In certain embodiments, the medium chain fatty acids are predominantly saturated, i.e., greater than about 60%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, or greater than about 95% saturated. In particular embodiments, the solubilizing agent comprises a mixed triglyceride predominantly comprising C8 and C10 fatty acids. In other particular embodiments, the solubilizing agent comprises both simple and mixed triglycerides predominately comprising C8 and C10 fatty acids. In particular embodiments, the solubilizing agent comprises a mixed triglyceride predominantly comprising saturated C8 and C10 fatty acids. In other particular embodiments, the solubilizing agent comprises both simple and mixed triglycerides predominately comprising saturated C8 and C10 fatty acids.

In some embodiments, the solubilizing agent/carrier is selected to enhance dissolution or suspension of progesterone. In further various embodiments, the solubilizing agent/carrier is selected to enhance absorption of the API by cells of a mammal. For example, certain carriers may be selected to enhance absorption of the other formulation components, including the API. Absorption may comprise absorption into any cell and particularly absorption into digestive system cells, such as intestinal cells, and cells of the female reproductive system, such as the vagina and the cervix. Selected mono-, di-, or triglycerides are particularly suited to aid in cellular absorption.

In certain embodiments, a surfactant is used to aid in solubilizing, partially solubilizing, or suspending progesterone in the solubilizing agent. For example, a surfactant, such as GELUCIRE 44/14, can be used. In certain embodiments, GELUCIRE 44/14 may be heated to approximately 45-50° C. When the surfactant is completely melted, it is added to an appropriate container that contains the solubilizing agent. The solubilizing agent and surfactant are mixed. During this mixing process the progesterone is added, thus, solubilizing, partially solubilizing, or suspending progesterone. In certain embodiments, the solubilizing agent is liquid at between room temperature and about 50° C., at or below 50° C., at or below 40° C., or at or below 30° C.

In various embodiments, the solubilizing agent/carrier can be an oil having medium chain fatty acids as a majority or predominant component. Suitable medium chain fatty acids include caproic acid (C6), enanthic acid (C7), caprylic acid (C8), pelargonic acid (C9), capric acid (C10), undecylic acid (C11), lauric acid (C12), tridecyllic acid (C13), and myristic acid (C14). In use, these fatty acids are predominantly saturated (e.g., greater than 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than

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about 90%, or greater than about 95%, or about 100%). In certain embodiments, predominantly C6 to C12 saturated fatty acids are contemplated. In certain embodiments, predominately C8 to C10 saturated fatty acids are contemplated. In certain embodiments, these fatty acids may be bound to glycerin, propylene glycol, ethylene glycol, or polyethylene glycol. In certain embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent.

10 In particular embodiments, the solubilizing agent can comprise a mixture of caprylic/capric triglycerides; caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; caprylic/capric/succinic triglycerides; propylene glycol dicaprylate/dicaprate; and combinations and derivatives thereof. In further embodiments, in addition to the various mixtures of the specified triglycerides, the solubilizing agent can further include polyethylene glycol.

Suitable carriers/solubilizing agents further include esters of saturated coconut and palm kernel oil and derivatives 20 thereof, including fractionated coconut oils and palm kernel oils; and triglycerides of fractionated vegetable fatty acids, and derivatives thereof and combinations thereof. In further various embodiments, the carrier/solubilizing agent may comprise one or more monoglycerides, diglycerides, triglycerides, and combinations thereof having predominately 25 C6-C12 fatty acid esters. Specifically contemplated as the solvent are mono-, di-, and triglycerides of saturated C8-C10 (caprylic/capric) fatty acids. Exemplary glycerin based solubilizing agents include MIGLYOLS®, which are caprylic/capric triglycerides (SASOL Germany GMBH, Hamburg). MIGLYOLS includes MIGLYOL 810 (caprylic/capric triglyceride), MIGLYOL 812 (caprylic/capric triglyceride), MIGLYOL 816 (caprylic/capric triglyceride), and MIGLYOL 829 (caprylic/capric/succinic triglyceride). Other 30 caprylic/capric triglyceride solubilizing agents are likewise contemplated, including, for example: caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; caprylic/capric/succinic triglycerides. In certain 35 embodiments, CAPMUL MCM, medium chain mono- and di-glycerides of caprylic/capric fatty acids, is the solubilizing agent. In other embodiments, CAPMUL PG-8 (Propylene Glycol Monocaprylate), CAPMUL PG-10 (Propylene Glycol Monocaprate), or other caprylic/capric CAPMULs is the solubilizing agent. Triglycerides of fractionated 40 vegetable fatty acids, and combinations or derivatives thereof 45 can be the solubilizing agent, in certain embodiments.

Additional examples of solubilizing agents include a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the CAPMUL brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; 50 propylene glycol dicaprylate; a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol (also referred to as TRANSCUTOL®); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL and MIGLYOL; TRANSCUTOL, MIGLYOL and CAPMUL PG-8 or 55 CAPMUL PG-10; CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM and a non-ionic surfactant; and CAPMUL MCM and GELUCIRE.

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In particular embodiments, the solubilizing agent comprises combinations of mono- and di-esters of propylene glycol or ethylene glycol or mono-, di-, and triglyceride combinations.

In certain embodiments, polyethylene glycol glyceride (GELUCIRE®, GATTEFOSSE SAS, Saint-Priest, France) can be used as the solubilizing agent or as a surfactant. For example, GELUCIRE 44/14 can be used. GELUCIRE 44/14 is a non-ionic water dispersible surfactant, also known as lauroyl macrogol-32 glycerides EP and lauroyl polyoxyl-32 glycerides NF. For example, in certain embodiments, a non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, such GELUCIRE 44/14 (discussed previously herein), GELUCIRE 44/11, GELUCIRE 39/01 (glycerol esters of saturated C12-C18 fatty acids), GELUCIRE 43/01 (hard fat NF/JPE), GELUCIRE 50/13 (stearoyl macrogol-32 glycerides EP, stearoyl polyoxyl-32 glycerides NF, and stearoyl polyoxylglycerides (USA FDA IIG)). These surfactants may be used at concentrations greater than about 0.01 wt. %, and typically in various amounts of about 0.01 wt. %; about 10.0 wt. %; about 10.1 wt. %; about 20 wt. %; about 20.1 wt. %; and about 30 wt. %. More specifically, these surfactants may be used at concentrations between 0.01 wt. % to 5.00 wt. %.

Other non-ionic surfactants include, for example and without limitation one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In other embodiments, non-ionic surfactants can comprise polyethylene sorbitol esters, such as polysorbate 80, which is commercially available under the trademark TWEEN® 80 (polysorbate 80) (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50% of the pharmaceutical composition by mass, and in particular embodiments, about 30% of the pharmaceutical composition total mass.

Yet another non-ionic surfactants is PEG-6 palmitostearate and ethylene glycol palmitostearate, which is available commercially as TEFOSE® 63 (GATTEFOSSE SAS, Saint-Priest, France), which can be used with, for example, CAPMUL MCM having ratios of MCM to TEFOSE 63 of, for example, 8:2 or 9:1. In other embodiments, other solubilizing agents/non-ionic surfactants combinations include, for example, MIGLYOL 812: GELUCIRE 50/13 or MIGLYOL 812: TEFOSE 63.

In still further embodiments, the surfactant can be an anionic surfactant, for example: ammonium lauryl sulfate, dioctyl sodium sulfosuccinate, perfluoro-octane sulfonic acid, potassium lauryl sulfate, or sodium stearate.

In certain embodiments, the non-ionic or anionic surfactant(s) can be used alone with at least one solubilizing agent or can be used in combination with other surfactants. Accordingly, such surfactants, or any other excipient as set forth herein, may be used to solubilize one or more APIs. In this disclosure, the API is progesterone. The combination of solubilizing agent, surfactant, and other excipients should be designed whereby the one or more APIs are delivered to the target tissue and result the intended effect of the API.

Various ratios of the noted solubilizing agents can be used for suspension or solubilization of progesterone. CAPMUL MCM and a non-ionic surfactant, e.g., GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 9:1, 7:3, 6:4, and 6:3 when progesterone is the sole API and at ratios of 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10 with estradiol as the sole API.

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Other non-limiting examples include CAPMUL MCM and GELUCIRE 44/14 used in ratios including, for example, and without limitation, 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1; CAPMUL MCM and GELUCIRE 39/01 can be used in ratios including, for example and without limitation, 6:4, 7:3, and 8:2 (one or more API composition); CAPMUL MCM and GELUCIRE 43/01 can be used in ratios including, for example and without limitation, 7:3, and 8:2 (one or more API composition); and CAPMUL MCM and GELUCIRE 50/13 can be used in ratios including, for example and without limitation, 7:3, and 8:2, and 9:1. In other embodiments, CAPMUL MCM and GELUCIRE were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be, e.g., 8:1 or greater, e.g., 60 to 70:1.

Combinations of these solubilizing agents can produce solubilized or partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments, solubilizing agents used to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, ethylene glycol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, progesterone is soluble in the oils at room temperature, although it may be desirable to warm certain oils initially during manufacture to improve viscosity. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 30° C. In illustrative embodiments, GELUCIRE 44/14 is heated to about 65° C. and CAPMUL MCM is heated to about 40° C. to facilitate mixing of the oil and non-ionic surfactant, although such heating is not necessary to dissolve the estradiol or progesterone.

In illustrative embodiments, the solubility of estradiol in the solubilizing agent or combination of solubilizing agents is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher. Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, CAPMUL MCM, CAPMUL MCM C10 (Glyceryl Monocaprate), CAPMUL MCM C8 (Glyceryl Monocaprylate), and CAPMUL MCM C8 EP (Glyceryl Monocaprylate). These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, MIGLYOL 810 and MIGLYOL 812.

Illustrative examples of solubilizing agents that are medium chain fatty acid esters of propylene glycol include, among others, CAPMUL PG-8, CAPMUL PG-2L EP/NF (Propylene Glycol Dilaurate), CAPMUL PG-8 NF (Propylene Glycol Monocaprylate), CAPMUL PG-12 EP/NF (Propylene Glycol Monolaurate) and CAPRYOL (Propylene glycol monocaprylate (type II) NF). Other illustrative examples include MIGLYOL 840 (Propylene Glycol Dicaprylate/Dicaprate).

Illustrative examples of solubilizing agents that are medium chain fatty acid esters of polyethylene glycol include, among others, GELUCIRE 44/14 (PEG-32 glyceryl

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laurate EP), which is polyethylene glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of GELUCIRE, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. In particular embodiments, the predominantly C8 to C12 saturated fatty acids comprise not less than 50 wt %, not less than 75 wt %, not less than 85 wt %, not less than 90 wt %, or not less than 95 wt % of the solubilizing agent.

It will be understood that commercially available fatty acid esters of glycerol and other glycols are often prepared from natural oils and therefore may comprise components additional to the fatty acid esters that comprise the predominant (by weight) component(s) and that therefore are used to characterize the product. Such other components may be, e.g., other fatty acid triglycerides, mono- and diesters, free glycerol, or free fatty acids. So, for example, when an oil/solubilizing agent is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for CAPMUL MCM C8 describes CAPMUL MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

By way of further example, MIGLYOL 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

Specifically, a product information sheet for MIGLYOL by SASOL provides the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in C8-C10 triglycerides, and a thickening agent, it will be understood that the fatty acid esters component of the formulation may be, e.g., MIGLYOL 812 or a similar product.

By way of further illustration, GELUCIRE 44/14 is generally described as lauroyl polyoxyl-32 glycerides, i.e., polyoxyethylene 32 lauric glycerides (which is a mixture of mono-, di-, and triesters of glycerol and mono- and diesters

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of PEGs) because the fatty acid composition is 30 to 50% lauric acid and smaller amounts of other fatty acids, e.g., up to 15% caprylic acid, up to 12% capric acid, up to 25% myristic acid, up to 25% palmitic acid, and up to 35% stearic acid. The product may also contain small amounts of non-esterified glycols.

Similarly, where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, it will be understood that the thickening agent component of the formulation may be, e.g., TEFOSE 63 (PEG-6 palmitostearate and ethylene glycol palmitostearate) or a similar product.

In illustrative embodiments of the invention, the selected solubilizing agent does not require excessive heating in order to solubilize progesterone. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL MCM) and polyethylene glycol glycerides (e.g., GELUCIRE) as a surfactant, the oil or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The progesterone can be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

In various embodiments, a lubricant is used. Any suitable lubricant may be used, such as, for example and without limitation, lecithin, and in various embodiments, a mixture of polyethylene glycol ("PEG") esters, glycerides, and PEG, such as is commercially available under the trade name GELUCIRE (Gattefosse, FR) may also be used as a lubricant. Suitable lubricants may also comprise calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, poloxamer, glycals, and phospholipid mixtures. In particular, a mixture of polyethylene glycol esters, glycerides, and PEG such as GELUCIRE 44/14, may be used as a lubricant. GELUCIRE 44/14 is a non-ionic water dispersible surfactant, also known as lauroyl macrogol-32 glycerides EP and lauroyl polyoxyl-32 glycerides NF. In various embodiments, GELUCIRE 44/14 acts as a suspension agent.

In various embodiments, an antioxidant is used. Any suitable antioxidant may be used, such as, for example and without limitation, butylated hydroxytoluene, also commercially referred to as BHT. Butylated hydroxytoluene, a derivative of phenol, is lipophilic and is thus suited to being intermixed with ultra-micronized progesterone and carriers disclosed or contemplated herein.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% solubilizing agent by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

In certain embodiments, the pharmaceutical composition further comprises at least one thickening agent. Generally, a thickening agent is added when the viscosity of the pharmaceutical composition provides less than desirable absorption following administration. Examples of thickening agents include: hard fats; propylene glycol; a mixture of hard fat EP/NF/JPE, glyceryl ricinoleate, ethoxylated fatty alcohols (ceteth-20, steareth-20) EP/NF (available as OVUCIRE® 3460, GATTEFOSSE, Saint-Priest, France); a mixture of hard fat EP/NF/JPE, glycerol monooleate (type 40) EP/NF (OVUCIRE WL 3264; a mixture of hard fat EP/NF/JPE, glyceryl monooleate (type 40) EP/NF (OVUCIRE

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WL 2944); and a mixture of various hard fats (WITEP-SOL®, Sasol Germany GmbH, Hamburg, Germany). In certain embodiments, the viscosity of pharmaceutical compositions in accordance with various embodiments may comprise from about 50 cps to about 1000 cps at 25° C. A person of ordinary skill in the art will readily understand and select from suitable thickening agents.

In other embodiments, the thickening agent is a non-ionic surfactant. For example, polyethylene glycol saturated or unsaturated fatty acid ester or diester is the non-ionic surfactant thickening agent. In some embodiments, the non-ionic surfactant comprises a polyethylene glycol long chain (C16-C20) fatty acid ester and further comprises an ethylene glycol long chain fatty acid ester, such as PEG-fatty acid esters or diesters of saturated or unsaturated C16-C18 fatty acids, e.g., oleic, lauric, palmitic, and stearic acids. In embodiments, the non-ionic surfactant comprises a polyethylene glycol long chain saturated fatty acid ester and further comprises an ethylene glycol long chain saturated fatty acid ester, such as PEG- and ethylene glycol-fatty acid esters of saturated C16-C18 fatty acids, e.g., palmitic and stearic acids. Such non-ionic surfactant can comprise PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, such as but not limited to TEFOSE 63.

In certain embodiments, the non-ionic surfactant used as a thickening agent is not hydrophilic and has good emulsion properties. An illustrative example of such surfactant is TEFOSE 63, which has a hydrophilic-lipophilic balance (HLB) value of about 9-10.

The selection and amount of hydrophilic polymer may be based on the selection and amount of solubilizing agent. The pharmaceutical composition can include a hydrophilic polymer but optionally excludes a gelling agent. In embodiments having a hydrogel, from about 5% to about 10% of the total mass may comprise the hydrophilic polymer. In further embodiments, hydrogels may be employed. A hydrogel may comprise chitosan, which swell in response to contact with water. In various embodiments, a cream pharmaceutical composition may comprise PEG-90M.

In addition to the above, the pharmaceutical compositions described herein can include one or more thermoreversible gels, typically of the hydrophilic nature including for example and without limitation, hydrophilic sucrose and other saccharide-based monomers (U.S. Pat. No. 6,018,033, which is incorporated herein by reference).

The choice of excipient will depend on factors such as, for example, the effect of the excipient on solubility and stability. Additional excipients used in various embodiments may include colorants, flavoring agents, taste-masking agents and preservatives. In certain embodiments, colorants, comprise about 0.1% to about 2% of the pharmaceutical composition by weight. In certain embodiments, preservatives in the pharmaceutical composition comprise methyl and propyl paraben, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Generally, the solubilizing agents, excipients, other additives used in the pharmaceutical compositions described herein, are non-toxic, pharmaceutically acceptable, compatible with each other, and maintain stability of the pharmaceutical composition and the various components with respect to each other. Additionally, the combination of various components that comprise the pharmaceutical compositions will maintain will result in the desired therapeutic effect when administered to a subject.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the

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nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of this disclosure are generally orally administered, typically via, for example, capsules such as soft capsules.

In certain embodiments, a pharmaceutical composition of this disclosure comprises progesterone, (with about 15% or less, and in particular embodiments, about 5% or less of the progesterone being solubilized—the balance being ultra-micronized/suspended as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of one or more glycols, with or without surfactant.

Pharmaceutical formulations in accordance with various embodiments comprise ultra-micronized progesterone. In further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, and a lubricant. In still further embodiments a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, a lubricant, and optionally an antioxidant. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and a medium chain triglyceride as a carrier. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and mono-, di-, or triglycerides of caprylic/capric acid as a carrier. Various further embodiments also comprise lecithin and optionally butylated hydroxytoluene.

In additional embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone and at least one carrier, a lubricant, optionally an antioxidant, and other pharmaceutically acceptable excipients. For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

According to embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, at least one carrier, and a non-ionic surfactant.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives, and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

In various embodiments, ultra-micronized progesterone is administered in a capsule. Capsules may be prepared using one or more film forming polymers. Suitable film forming polymers include natural polymers, such as gelatin, and synthetic film forming polymers, such as modified celluloses. Suitable modified celluloses include, but are not limited to, hydroxypropyl methyl cellulose, methyl cellulose.

Manufacturing

In certain embodiments, the pharmaceutical composition is prepared by blending progesterone with a pharmaceutically acceptable solubilizing agent, including for example and without limitation, at least one medium chain fatty acid

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such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. In particular embodiments, the pharmaceutical composition also comprises at least one glycol or derivatives thereof or combinations thereof or combinations of at least one glyceride and glycol. The glycol(s) may be used as solubilizing agents or to adjust viscosity and, thus, may be considered thickening agents. Other excipients can optionally be included, including, for example and without limitation, anti-oxidants, lubricants, and the like. In some embodiments, the pharmaceutical composition includes sufficient solubilizing agent(s) to fully solubilize the progesterone. It is expressly understood, however, that other volumes of solubilizing agent can be used depending on the level of progesterone solubilization desired. Persons of ordinary skill in the art will know and understand how to determine the volume of solubilizing agent and other excipients depending on the desired percent of progesterone to be solubilized in the pharmaceutical composition.

In illustrative embodiments, GELUCIRE 44/14 (lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, lauroyl polyoxylglycerides (USA FDA IIG)) is heated to about 45-65° C. and CAPMUL MCM or MIGLYOL 812 is heated to about 40° C. to facilitate mixing of the oil and non-ionic surfactant, although such heating is not necessary to dissolve the progesterone.

Specific Examples disclosed herein provide additional principles and embodiments illustrating processes for manufacturing the pharmaceutical compositions disclosed herein.

Delivery Vehicle

The pharmaceutical compositions described herein can be delivered orally inside of a delivery vehicle, for example a capsule. In certain embodiments, the capsules are soft capsules made of materials well known in the pharmaceutical arts such as gelatin. In other embodiments, the delivery vehicle is integral with the pharmaceutical composition (i.e., the pharmaceutical composition is the delivery vehicle). Hard or soft shell capsules can be used to administer the API. In certain embodiments, capsules may be prepared by forming the two capsule halves, filling one of the halves with a fill solution, and then sealing the capsule halves together to form the finished capsule.

Hard shell capsules may be prepared by combining the "Body" and the "Cap". The "Body" of the capsule is filled with the "fill mass" and then closed with the "Cap". The "Body"/"Cap" interface is then sealed/banded.

Soft gelatin ("softgel") capsules may be prepared using a rotary die encapsulation process, as further described below. Softgel capsules may contain the formulation disclosed herein as a "fill material." The soft gelatin capsule do not contain one or more of the following as the fill material: hydrophilic gel-forming bioadhesive (e.g., mucoadhesive) agents; a lipophilic agent and a gelling agent for the lipophilic agent, or a hydrodispersible agent. In some embodiments, the hydrophilic gel-forming bioadhesive agent is carboxyvinyllic acid; hydroxypropylcellulose; carboxymethylcellulose; gelatin; xanthane gum; guar gum; aluminum silicate; or mixtures thereof. In still other embodiments, the lipophilic agent is a liquid triglyceride; solid triglyceride (e.g., with a melting point of about 35° C.); carnauba wax; cocoa butter; or a mixture thereof. In certain embodiments, the gelling agent is a hydrophobic colloidal silica. And in still other embodiments, the hydrodispersible agent can be polyoxyethylene glycol; polyoxyethylene glycol 7-glycerylcocoate; or a mixture thereof.

The softgel capsule itself may comprise a gelatin material in a relatively solid or stiff form. The gel capsule defines an

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inner volume that contains the fill material. Dissolution of the gelatin material may commence at various points after administration, such as in the digestive tract (mouth, esophagus, stomach and intestines), or in another body cavity, such as the vaginal tract.

Gel capsules may be prepared using one or more film forming polymers. Suitable film forming polymers include, but are not limited to, natural polymers, such as gelatin, and synthetic film forming polymers, such as modified celluloses. Suitable modified celluloses include, but are not limited to, hydroxypropyl methyl cellulose, methyl cellulose.

Suitable shell additives, for either a hard or soft shell capsules, may include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids, and combinations thereof. The main ingredients of the capsule shell is primarily gelatin (or a gelatin substitute for non-gelatin capsules), plasticizer, and purified water. Hard shell and soft shell capsules differ primarily in the amount of plasticizer present that is used in the capsule shell.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include, but are not limited to, glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light-sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to minimize cross-linking of the gelatin.

In accordance with various embodiments, a softgel dosage form is used.

As the softgel dissolves, the inner volume may come into fluid communication with the digestive system, allowing the fill material to leach outside the softgel. A softgel may also be punctured, cut, or otherwise opened outside a body. The fill material may then be poured or squeezed outside the gel capsule and applied on or in the body, such as within the vaginal cavity.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin, sorbitol, propylene glycol, microcrystalline cellulose, silica, mineral oil, and combinations thereof which are often components of the plasticizer composition. Regulated water activity in pharmaceutical compositions and dosage forms, such as capsules, can improve the compatibility and stability of the compositions and forms. This is because when hydrolysis is regulated chemical degradation caused by water is also regulated (or slowed, as is desirable in the present case). Thus, by regulating water in the present compositions, the capsule shells are less likely to soften, dissolve, break, or leak during storage. Moreover, due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hy-

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droxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl esters (collectively known as “parabens”) or combinations thereof.

The fill material may comprise a liquid, such as an oil, a solution, a suspension, or other acceptable forms. The active ingredient or active ingredient may be contained within the liquid.

Hard and softgel capsules can be manufactured according to various techniques known in the art. In particular embodiments, softgel capsules can be prepared using a rotary die encapsulation process. An exemplary process is disclosed in Wilkinson, P. K. et al., 1990, “Softgels: manufacturing considerations.” In: Specialized Drug Delivery Systems, P. Tyle (Ed.), pp. 409-449, Marcel Dekker, Inc., New York, the entirety of which is hereby incorporated by reference.

In other embodiments, softgels can be prepared according to the process disclosed in PCT/US2000/005178, the entirety of which is incorporated herein by reference.

Hard shell capsules can also be used as the delivery vehicle. These capsules may be prepared by forming the two capsule halves, filling one half with the fill material, and then sealing the halves together to form the finished capsule. In other embodiments, hard shell capsules may be prepared by combining a “body” and a “cap.” The “body” of the capsule is filled with the fill material and then closed with the cap. The body/cap interface is then sealed or banded.

DRAWINGS

Methods of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material, i.e. fill mass, preparation 100 is shown. Operation 102 comprises mixing a solubilizing agent, a surfactant (i.e. lubricant), and an antioxidant as described herein. For example, lecithin and butylated hydroxytoluene may be mixed with one or more medium chain mono-, di- or triglycerides, or combinations thereof. Mixing may be facilitated by an impellor, agitator, or other suitable means. Operation 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Operation 104 may comprise mixing progesterone (progesterone) into the mixture of the solubilizing agent, the surfactant (i.e. lubricant), and the antioxidant. A pasty substance is thus formed. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Operation 104 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Operation 106 comprises degassing. The resulting mixture from operation 106 may comprise a pharmaceutical composition suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e., gel mass, production 200 is shown. Operation 202 comprises mixing glycerin with water. The water used in operation 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Operation 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80°±5° C.

Operation 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Operation 204 may be performed under an inert or relatively inert gas

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atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in operation 204 to de-aerate.

Operation 206 comprises addition of an excipient (i.e. coloring agent) such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or the suitable agent. Operation 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Operation 208 comprises degassing. The resulting mixture from operation 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Operation 302 comprises heating the fill material. The pharmaceutical composition may be heated to any suitable temperature. In various embodiments, the pharmaceutical composition is heated to 30° C.+/-3° C. pharmaceutical composition maybe heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the pharmaceutical composition or to dispense the pharmaceutical composition in controlled volumes.

Operation 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in operation 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the pharmaceutical composition within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812. Operation 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85±0.05 mm using spreader box knobs. The pharmaceutical composition may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Operation 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Polishing may be performed with isopropyl alcohol.

Design Factors for Encapsulated Pharmaceutical Compositions

In certain embodiments, the pharmaceutical composition is designed to maximize API solubility, and other favorable characteristics without sacrificing efficacy, while simultaneously improving bioavailability in subjects. Other favorable characteristics, besides improving bioavailability as compared to the RLD, include, for example, bioavailability that is bioequivalent to the RLD, improved subject compliance (i.e., ability to easily take the right capsule during the correct period), reducing food and allergy effects due to administration, and reducing required prescribed dosage levels in order to achieve efficacy of the drug product.

In some embodiments, progesterone is fully or partially solubilized. The form of the API (i.e., being in solution), and other factors and conditions, may account for the increased bioavailability of progesterone as compared to the RLD.

In some embodiments, the pharmaceutical composition is delivered via a gelatin capsule delivery vehicle. In these embodiments, the pharmaceutical composition is a liquid pharmaceutical composition. Accordingly, the pharmaceutical composition of such embodiments is encapsulated in the gelatin capsule. The inclusion of the capsules in blister

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packs, as described elsewhere herein, ensures that subjects will receive the right dosage during the correct period of time.

In some embodiments, the gelatin capsules are softgels. Other forms of administration (i.e. injection, intra-muscular, etc.) can cause pain, discomfort, or irritation, especially when frequent administration is required. Softgels eliminate these problems, while minimizing adverse tastes. Softgels can be administered orally or can be administered locally. In some embodiments, the softgel is administered orally.

Through extensive experimentation, various medium chain fatty acid esters of glycerol and propylene glycol demonstrated one or more favorable characteristics for development as a human drug product. In one embodiment, the solubilizing agent was selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di-, or triglyceride and glycols, and combinations thereof.

In other embodiments, the solubilizing agent was selected from one or more C6 to C12 fatty acid mono-, di-, or triesters of glycerol, e.g., one or more C6 to C14 triglycerides, e.g., one or more C6 to C12 triglycerides, such as one or more C8-C10 triglycerides. Thus, in certain embodiments, the pharmaceutical composition comprises progesterone that is at least about 75% solubilized in a solubilizing agent comprising one or more C6 to C14 medium chain fatty acid mono-, di-, or triglycerides and, optionally, a thickening agent.

In still other embodiments, the pharmaceutical composition comprises progesterone that is at least about 75% solubilized one or more C6 to C12 medium chain fatty acid mono-, di-, or triglycerides, e.g., one or more C6 to C14 triglycerides, e.g., one or more C6 to C12 triglycerides, such as one or more C8-C10 triglycerides. These embodiments specifically contemplate the progesterone being at least 85% solubilized, at least 90% solubilized, at least 95% solubilized, and in certain instances, 100% solubilized. In other embodiments, estradiol or a combination of progesterone and estradiol is included in the pharmaceutical compositions as the one or more APIs.

As noted previously herein, liquid pharmaceutical compositions are preferably liquid at room temperature. Accordingly, gels, hard fats, or other solid forms that are not liquid at room or body temperature are less desirable in embodiments of the pharmaceutical composition that are liquid. In certain embodiments, where a non-ionic surfactant such as GELUCIRE or TEFOSE to increase viscosity, the non-ionic surfactant may be solid at room temperature. In those situations, the non-ionic surfactant may require melting to mix with one or more APIs solubilized in a fatty acid-glycol ester. In this embodiment, the resultant composition is advantageously liquid, not solid. However, in these embodiments, the resultant pharmaceutical composition remains liquid, albeit with greater viscosity, although it is still not a solid.

In other embodiments, the pharmaceutical composition comprises progesterone, a medium chain solubilizing agent, and a thickening agent as the only essential ingredients delivered via a softgel delivery vehicle. Non-essential ingredients, e.g., colorants, antioxidants, preservatives, or other excipients may be included as well. Other embodiments comprise one or more APIs.

Additional ingredients can be incorporated in amounts that do not materially change the solubility of the progesterone, the pharmacokinetics of the pharmaceutical composition, or the efficacy of the pharmaceutical composition. Other factors that should be considered when adjusting the

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ingredients of the pharmaceutical composition include taste, water regulation, and other relevant factors, for example those that would lead to reduced patient compliance.

In softgel embodiments, mucoadhesive agents, gelling agents, dispersing agents, or the like would not be included because of effects some of these ingredients may have on bioavailability of the API(s) in the digestive system.

Methods

Pharmaceutical compositions in different embodiments

10 may be administered alone or combination with one or more other drugs (or as any combination thereof). For example, compositions in accordance with embodiments including one or more other drugs may also comprise estradiol. In such compositions, estradiol is also an API.

15 In certain embodiments, and as discussed elsewhere herein, the pharmaceutical composition disclosed herein can be administered orally in a softgel. As the softgel dissolves after administration, the inner volume may come into fluid communication with the digestive system such that the

20 progesterone present in the pharmaceutical composition can be absorbed systemically. Oral administration may involve swallowing, so that the pharmaceutical composition enters the gastrointestinal tract. Alternatively, buccal or sublingual administration may be employed such that the pharmaceutical composition enters the bloodstream directly from the mouth.

25 In embodiments where hard shell capsules are employed, the method of administration is typically oral. Hard capsules or softgels may be arranged in blisters or cartridges or bottles.

30 In certain embodiments, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having delivery days identified to improve subject compliance. One or more of the capsules may contain no progesterone. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each dose (e.g., each softgel) may contain solubilized, partially solubilized, or 35 partially suspended progesterone in any of the amounts previously set forth herein, though may, in certain instances, include 100, 150, or 200 mg of progesterone. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such 40 blister packs may contain any number of capsules.

45 In additional embodiments, progesterone is formulated for intraperitoneal, percutaneous, subcutaneous, intra-muscular, and atomization administration (i.e. such as with nasal mist administration).

50 In still other embodiments, the pharmaceutical compositions are administered according to other techniques known to those skilled in the art, which may include, but are not limited to: tablets, film-coated tablets, prolonged-release tablets, modified-released tablets, effervescent tablets, orodispersible tablets, sachets, dry powders used to form suspension; or liquid dosage forms.

55 Compositions in accordance with the various embodiments disclosed herein may be used to treat or prevent endometrial hyperplasia, prevent secondary amenorrhea, or mitigate or treat the effects of estradiol supplementation. In certain embodiments, compositions comprising progesterone may be co-administered with estradiol or co-formulated with estradiol.

60 In other embodiments, formulations in accordance with various embodiments may be used to treat or prevent preterm delivery in pregnant women, including in certain women having a shortened cervix. In various embodiments,

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a capsule, for example a softgel capsule, may be opened and the fill material applied in or around the vagina. However, in various embodiments the capsules are taken orally.

In still further embodiments, formulations in accordance with various embodiments may be used to treat menopause-related symptoms, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy; and osteoporosis and endometrial hyperplasia reduction.

In still further embodiments, formulation in accordance with various embodiments may be used to treat amenorrhea.

Additional objects of this disclosure include: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

Enhanced Bioavailability

In certain embodiments, the formulations disclosed herein provide enhanced bioavailability of progesterone when compared to conventional progesterone formulations. As a result of this improved bioavailability, certain embodiments of the formulations disclosed herein allow for a reduction in the quantity of progesterone administered to a person in need thereof while still providing the benefits of a dosage form containing the greater amount of progesterone.

As such, and in certain embodiments, a formulation of this disclosure can include less than 200 mg of progesterone while still having an acceptable PK profile. In particular, embodiments, the formulation can include about 175 mg of progesterone, about 170 mg of progesterone, about 165 mg of progesterone, about 160 mg of progesterone, about 159 mg of progesterone, about 158 mg of progesterone, about 157 mg of progesterone, about 156 mg of progesterone, about 155 mg of progesterone, about 154 mg of progesterone, about 153 mg of progesterone, about 152 mg of progesterone, about 151 mg of progesterone, about 150 mg of progesterone, about 149 mg of progesterone, about 148 mg of progesterone, about 147 mg of progesterone, about 146 mg of progesterone, about 145 mg of progesterone, about 170 mg of progesterone, about 140 mg of progesterone, about 135 mg of progesterone, about 170 mg of progesterone, about 130 mg of progesterone, about 125 mg of progesterone, about 120 mg of progesterone, about 115 mg of progesterone, about 110 mg of progesterone, about 105 mg of progesterone, or about 100 mg of progesterone. In still further embodiments, the formulation can have exactly the amounts of progesterone noted above, e.g. exactly 175 mg of progesterone, exactly 170 mg of progesterone, etc.

In certain embodiments, this disclosure provides a formulation including less than 200 mg of progesterone having an $AUC_{0-\infty}$ in (ng/ml)*hr of from about 5 to about 500, from about 5 to about 400, from about 5 to about 300, from about 5 to about 270, from about 20 to about 200, from about 25 to about 150, or from about 25 to about 140. In particular embodiments, the formulation including less than 200 mg progesterone can have an $AUC_{0-\infty}$ of about 137 (ng/ml)

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*hr \pm 95%. In particular embodiments, the formulation can have about 150 or exactly 150 mg progesterone.

In certain embodiments, this disclosure provides a formulation including less than 200 mg of progesterone having an $AUC_{0-\infty}$ in (ng/ml)*hr of from about 5 to about 500, from about 5 to about 400, from about 5 to about 300, from about 5 to about 240, from about 20 to about 200, from about 25 to about 150, or from about 25 to about 140. In particular embodiments, the formulation including less than 200 mg progesterone can have an $AUC_{0-\infty}$ of about 120 (ng/ml) *hr \pm 95%. In particular embodiments, the formulation can have about 150 or exactly 150 mg progesterone.

In certain embodiments, this disclosure provides a formulation including less than 200 mg of progesterone having a C_{max} in ng/ml of from about 3 to about 350, from about 3 to about 325, from about 3 to about 300, from about 3 to about 250, from about 3 to about 240, and from about 3 to about 230. In particular embodiments, the formulation including less than 200 mg progesterone can have a C_{max} of about 75 ng/ml \pm 95%. In particular embodiments, the formulation can have about 150 or exactly 150 mg progesterone.

Although the amount of progesterone is typically less than 200 mg, in certain embodiments, the amount of progesterone can be about 300 mg. In such embodiments, the formulation can have the PK parameters discussed below upon administration.

In certain embodiments, this disclosure provides a formulation including about 300 mg of progesterone having an $AUC_{0-\infty}$ in (ng/ml)*hr of from about 10 to about 1000, from about 10 to about 800, from about 10 to about 600, from about 10 to about 540, from about 40 to about 400, from about 50 to about 300, or from about 50 to about 280. In particular embodiments, the formulation including about 300 mg progesterone can have an $AUC_{0-\infty}$ of about 274 (ng/ml)*hr \pm 95%.

In certain embodiments, this disclosure provides a formulation including about 300 mg of progesterone having an AUC_{0-t} in (ng/ml)*hr of from about 10 to about 1000, from about 10 to about 800, from about 10 to about 600, from about 10 to about 480, from about 40 to about 400, from about 50 to about 300, or from about 50 to about 280. In particular embodiments, the formulation including about 300 mg progesterone can have an AUC_{0-t} of about 240 (ng/ml)*hr \pm 95%.

In certain embodiments, this disclosure provides a formulation including about 300 mg of progesterone having a C_{max} in ng/ml of from about 6 to about 700, from about 6 to about 650, from about 6 to about 600, from about 6 to about 500, from about 6 to about 480, and from about 6 to about 460. In particular embodiments, the formulation including about 300 mg progesterone can have a C_{max} of about 150 ng/ml \pm 95%.

55 Bioavailability comparisons to commercially available forms, such as tablet forms, may be determined by standard pharmacokinetic techniques.

In accordance with various embodiments, food effects are reduced, e.g., relative to comparative progesterone products.

60 In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Measurement of Efficacy

Efficacy can be measured using standard techniques known in the art. However in certain embodiments, subjects are administered progesterone. After administration of the progesterone, endometrial biopsies can be performed by a

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board-certified gynecologist. Procedures, instruments used, and observations are documented in the subject's file.

The resulting biopsy specimens can then be processed by a central laboratory. The central laboratory includes a chartered pathology committee of independent pathologists who are experts in the field of endometrial pathology to assess all endometrial biopsy sample.

In certain embodiments, treatment with the pharmaceutical compositions described herein resulted in complete and partial secretory activity. In cases of complete secretory activity, subjects experienced 1) glands with secretory changes, and 2) stromal predecidual changes. In cases of partial secretory activity, subjects experienced 1) glands with secretory changes, or 2) stromal predecidual changes.

In certain embodiments, subjects are administered pharmaceutical compositions as described herein, while other subjects are administered placebos. Exemplary test scenarios are described in the Example section, below. In these embodiments, secretory activity is measured as a proportion of subjects at Cycle 3 Day 24±1 day on active treatment (200 mg progesterone/day, 225 mg progesterone/day, or 300 mg progesterone/day) compared to placebo with complete secretory activity on endometrial biopsy (referenced in the examples as the "primary efficacy endpoint").

In these embodiments, secretory activity is also measured as a proportion of subjects at Cycle 3 Day 24±1 day on active treatment (200 mg progesterone/day, 225 mg progesterone/day, or 300 mg progesterone/day) compared to placebo with total secretory activity (defined as the aggregate of partial and complete secretory activity) on endometrial biopsy. Included in this measurement is an observation of the proportion of subjects reporting withdrawal bleeding at cycle 2 on or after cycle day 21 or within 7 days (including 7th day) after completion of blinded treatment at cycle 2 (this and the secretory measurement of the preceding sentence are referenced in the examples as the "secondary efficacy endpoints").

Statistical Measurements

Pharmacokinetics of the pharmaceutical composition disclosed herein can be calculated using statistical analyses. In particular embodiments, Analysis of Variance ("ANOVA") or Analysis of CoVariance ("ANCOVA") are used to evaluate differences between a subject receiving treatment with a pharmaceutical composition comprising an active pharmaceutical composition (for example, a pharmaceutical composition comprising progesterone) and a subject receiving treatment with a placebo (for example, the same pharmaceutical composition but without progesterone) or a reference drug. A person of ordinary skill in the art will understand how to perform statistical analysis of the data collected.

Among the data collected or calculated are PK parameters for pharmacokinetic evaluation and analysis, including, but not limited to, AUC, C_{max}, and T_{max}. The pharmacokinetic evaluation was carried out by a research lab using statistical and analytical software, which could include, but is not limited to, WinNonlin® software (version 5.3), and using SAS version 9.2.

SPECIFIC EMBODIMENTS

Through extensive trial-and-error testing of various fatty acid esters of glycerol and other glycols, embodiments of the invention have been invented that have one or more favorable characteristics for development as a human drug prod-

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uct. Such favorable characteristics include those described above, e.g., improved PK properties and reduced inter- and intra-patient variability.

Such embodiments include an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in ultra-micronized form suspended in a carrier that comprises a medium chain fatty acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester.

In particular embodiments, the progesterone can be ultra-micronized.

In certain embodiments, the progesterone is suspended or solubilized in one or more solubilizing agents such as one or more C6 to C14 fatty acid mono-, di-, or triesters of glycerol, including, but not limited to, one or more C6 to C14 triglycerides, one or more C6 to C12 triglycerides, or one or more C8-C10 triglycerides, as well as combinations thereof. An example of a solubilizing agent that provides beneficial properties is MIGLYOL, and in particular MIGLYOL 812.

In such general and more specific embodiments, the non-ionic surfactant is a polyethylene glycol saturated or unsaturated fatty acid ester or diester. In certain such embodiments, the non-ionic surfactant comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol. An example of a non-ionic surfactant that provides beneficial properties is GELUCIRE, e.g., GELUCIRE 44/14.

In certain such embodiments, the non-ionic surfactant has a HLB value of about 15. An illustrative example of such surfactant is GELUCIRE 44/14.

EXAMPLES

The formulations and methods described herein are now further detailed with reference to the following examples. These examples are provided for the purpose of illustration only and the formulations and methods described herein should in no way be construed as being limited to these examples. Rather, the formulations disclosed herein should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Example 1

In an exemplary embodiment, a capsule is provided containing a fill material comprising a formulation set forth in one of Tables 2, 2A, or 2B

TABLE 2

Ingredient	mg/Capsule	%	Function
Ultra-micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Solubilizing Agent
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

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TABLE 2A

Ingredient	mg/Capsule	%	Function
Progesterone	150	33.3	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	292.3	65.0	Solubilizing Agent
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	7.7	1.7	Lubricant/Emulsifier

TABLE 2B

Ingredient	mg/Capsule	%	Function
Progesterone	75	33.3	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	146.2	65.0	Solubilizing Agent
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.8	1.7	Lubricant/Emulsifier

The formulation in Table 2 is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

The formulations in Tables 2A and 2B are prepared as follows: melt Gelucire 44/14 by heating it to about 45-50° C.; once Gelucire 44/14 is completely melted, add MIGLYOL 812 and mix/stir until dissolved; continue mixing/stirring; during the mixing/stirring, slowly add progesterone to the solution; and, after all progesterone has been added, continue mixing for a period of time to ensure proper suspension and near dissolution equilibrium. The suspended progesterone is then passed through a colloid mill De-gassing and applying a vacuum for complete de-aeration of the fill mass is conducted. The resultant fill mass can be used for encapsulation.

Example 2

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 3

Ingredient	%	mg/Capsule	Function
Ultra-micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Solubilizing Agent
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

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In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

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Example 3

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be independently dissolved in a solubilizing agent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solubilizing agent; i.e., the solubility would be 50 mg to 100 mg per capsule.

MIGLYOL was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL, including without limitation MIGLYOL 812, may be used in embodiments comprising fully solubilized, partially solubilized, and suspended progesterone.

As can be seen in Table 4, the solubility of progesterone in CAPMUL MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization. Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Based on 95 mg/g solubility, a 50 mg progesterone capsule would require a 526 capsule size. The other capsule sizes required based on each respective solubility below includes: 1,799 mg, 579 mg, 709 mg, and 871 mg. Capsule size amounts based on respective solubilities will generally be at least 10% greater than the calculated value in order to ensure the progesterone remains in solution. Thus, a 50 mg progesterone capsule based on 73 mg/g solubility would require a 685 mg capsule, and with the at least 10% addition, it would require approximately a 754 mg sized capsule. Based on each respective solubility listed below, the capsule sizes include (approximately): 579 mg, 1799 mg, 637 mg, 780 mg, and 958 mg respectively. These values, and their corresponding 10% additions are shown in Table 4.

TABLE 4

55	Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM	73.4	
CAPMUL PG8	95	
MIGLYOL 812	27.8	
CAPMUL MCM:GELUCIRE 44/14 (9:1)	86.4	
CAPMUL MCM:GELUCIRE 44/14 (7:3)	70.5	
CAPMUL MCM:GELUCIRE 44/14 (6:3)	57.4	

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM in combination with GELUCIRE 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone or estradiol may be dissolved in

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a CAPMUL MCM and GELUCIRE 44/14 system, wherein the ratio of CAPMUL MCM to GELUCIRE 44/14 is 9:1.

TABLE 5

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM:GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM:GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM:GELUCIRE 44/14 (6:4)	57.4

Example 4

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 6

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Solubilizing Agent
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 7

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM)	394.0	65.67	Solubilizing Agent	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 5

In particular embodiments, a capsule is provided containing a pharmaceutical composition having fully solubilized,

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partially solubilized, or suspended progesterone comprising the components according to the formulations specified in Tables 8 and 9:

TABLE 8

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

TABLE 9

Ingredient	mg/Capsule	%	Function
Progesterone	200.00	33.33	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	389.60	64.93	Solubilizing Agent
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	10.00	1.67	Non-ionic Surfactant (suspending agent)
Butylated Hydroxytoluene	0.40	0.07	Antioxidant
Total	600.00	100.0	

The pharmaceutical composition above can be prepared in accordance with the procedures noted in prior examples.

Example 6

A gel mass can be prepared in order to encapsulate the pharmaceutical compositions of the various Examples herein.

Gel mass compositions were formulated and produced according to the following steps. Purified water (22.2 kg) and glycerin (10.8 kg) were charged into a stainless steel tank with mixing and heated to a temperature of 80±5° C. Hydrolyzed gelatin (1.8 kg) and gelatin 200 bloom limed bone, NF (24.0 kg) were then added to the water/glycerin mixture and were mixed until all solids were completely dissolved. This resulted in the formation of a gel mass. The

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resulting gel mass was de-gassed under vacuum. Coloring agents OPATINT® white (0.6 kg) and OPATINT® red (0.6 kg) were then added to the gel mass and the resultant was mixed for about 5 minutes. The resultant was then de-gassed under vacuum for a sufficient period of time and ultimately passed to an encapsulation device for preparation of gel capsules of the types disclosed herein.

Example 7

Bioavailability Assessment—Fasted

A randomized single-dose oral bioequivalence study comparing 200 mg ultra-micronized progesterone capsule test product (T) and 200 mg PROMETRIUM® (progesterone) capsules (Abbott Laboratories, Abbott Park, Ill.) reference product (R) is conducted. Subjects are administered a single 200 mg dose of either test product (T) or the reference product (R) under fasting conditions, for example, subjects fasted at least 10.0 hours prior to dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose.

Pharmacokinetic measurements are assessed including C_{max}, AUC and optionally T_{max}. Comparative bioavailability of the test product (T) and reference product are assessed.

Example 8

Bioavailability Assessment—Fed

The procedures for determining bioavailability under fasted conditions are repeated except that subjects are administered a single 200 mg dose of either test product (T) or reference product (R) immediately following a high fat meal, for example, within 30 minutes of dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose. Pharmacokinetic measurements are assessed including C_{max}, AUC and optionally T_{max}. Bioavailability of the test product (T) in reference to the reference product is assessed. The effect of food on the comparative bioavailability of the test product (T) and the reference product (R) are also assessed.

Example 9

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material, i.e. fill mass, preparation 100 is shown. Operation 102 comprises mixing a carrier, a lubricant, and an antioxidant as described herein. For example, lecithin and butylated hydroxytoluene may be mixed with one or more medium chain mono-, di- or triglycerides, or combinations thereof. Mixing may be facil-

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tated by an impellor, agitator, or other suitable means. Operation 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Operation 104 may comprise mixing ultra-micronized progesterone into the mixture of the carrier, the lubricant, and the antioxidant. A pasty substance is thus formed. 10 Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Operation 104 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Operation 15 106 comprises degassing. The resulting mixture from operation 106 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Operation 202 comprises mixing 20 glycerin with water. The water used in operation 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Operation 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80□±5□C.

30 Operation 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Operation 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in operation 204 to de-aerate.

35 Operation 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Operation 206 may be performed under an inert or relatively 40 inert gas atmosphere, such as nitrogen gas N₂. Operation 208 comprises degassing. The resulting mixture from operation 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

45 With reference to FIG. 3, softgel capsule assembly process 300 is shown. Operation 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C. +/- 3° C. Fill material maybe heated in a fill 50 hopper. A fill hopper may comprise a device configured to hold a volume of the fill material or to dispense the fill material in controlled volumes.

55 Operation 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in operation 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes 60 may be a temperature of 55° C. +/- 10° C. The wedge temperature may be 38° C. +/- 3° C. The drum cooling temperature may be 4° C. +/- 2° C. The encapsulator may be lubricated using MIGLYOL 812. Operation 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85±0.05 mm using spreader box knobs. The fill material may be injected into 65

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the gel to produce a fill weight having target weight $\pm 5\%$ (i.e., 650 ± 33 mg and 325 ± 16.3 mg).

Operation 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Polishing may be performed with isopropyl alcohol.

Example 10

Stability Study

In accordance with various embodiments, formulations in accordance with various embodiments have an exemplary shelf life of 3 months with storage at $25 \pm 2^\circ \text{C} / 60 \pm 5\% \text{ RH}$ in 75 cc HDPE white, opaque bottles with a 38/400 mm white child resistant cap.

Packaging during testing comprises a 75 cc round HDPE bottle and 33 mm cap. A Brasken FPT 300F resin is associated with the cap. Testing criteria include visual appearance, assay of progesterone, dissolution, content uniformity and microbial limits testing.

Three test groups are created. Test group 1 comprises a test at $40^\circ \text{C} / 75\% \text{ RH}$. Test group 2 comprises a test at $30^\circ \text{C} / 65\% \text{ RH}$. Test group 3 comprises a test at $25^\circ \text{C} / 60\% \text{ RH}$. Test group 1 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 1, 2, 3, and 6. Test group 2 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, and 12. Test group 3 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, 12 and 24.

Example 11

A particle size analysis is conducted by using a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the “Beckman Device”). The Beckman Device uses laser diffraction to determine particle size. A sample of a formulation in accordance with various embodiments is provided. The Beckman Device particle sensor yields that the sample has an X50 of $6.67 \mu\text{m}$, an X75 of $14.78 \mu\text{m}$, and an X25 of $2.193 \mu\text{m}$.

Example 12

A dissolution study was performed using a formulation in accordance with various embodiments. The results of the dissolution study are shown in FIG. 4.

The dissolution study was performed using a United States Pharmacopoeia dissolution apparatus 3 (reciprocating cylinder) (“USP Apparatus 3”). The USP Apparatus 3 was set to 30 dips per minute. Two hundred fifty mL (250 mL) of a solution of 1N HCl with 3% sodium lauryl sulfate was used at 37°C .

FIG. 4 shows dissolution percentage in the y axis over time in minutes on the x axis. A formulation in accordance with various embodiments is shown having circular dots, and is labeled formulation 402. An existing commercial pharmaceutical product containing progesterone is shown having square dots and is labeled existing product 404. As

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shown in FIG. 4, formulation 402 reaches a higher level of dissolution in a shorter time than existing product 404.

Example 13

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising ultra-micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of $4.279 \mu\text{m}$, an X75 of $7.442 \mu\text{m}$, and an X25 of $1.590 \mu\text{m}$. The Beckman Device also yielded that the mean particle size is $4.975 \mu\text{m}$, the median particle size is $4.279 \mu\text{m}$, the mode particle size is $6.453 \mu\text{m}$, and the standard deviation is $3.956 \mu\text{m}$. A graph of the particle distribution obtained is shown in FIG. 5.

Example 14

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of PROMETRIUM and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used.

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) (“USP Apparatus 3”). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37°C .

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from PROMETRIUM. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from PROMETRIUM is attached as FIG. 6.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

Example 15

Bioavailability & Bioequivalence Assessment

This study was conducted to determine bioavailability and bioequivalence of reference product PROMETRIUM “R” (200 mg progesterone) and test product “T” as described in Table 9 herein. T was administered as a softgel capsule.

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The study was an open-label, balanced, randomized, single-dose, two-treatment, three-period, three-sequence, crossover, partial replicate, reference-scaled oral bioequivalence study. A total of 72 healthy, adult, human, postmenopausal female subjects were enrolled in the study. Each subject was randomly assigned to a sequence (TRR, RTR, or RRT) such that each subject received T once and R twice during the course of the 32 day study (14 day washout between doses). R was administered twice so that the within subject variance could be calculated for later assessment of bioequivalence of the T and R formulations.

On study days 1, 15, and 29, patients who had been fasting for 10 hours were administered a high fat meal. 30 minutes after the meal, each patient was given a single softgel dose of T or, alternatively, R, in accordance with the patients' randomly assigned sequence. The dosage forms were taken with 240 ml of water. Subjects were housed in a clinical facility for at least 11 hours prior to dosing to at least 24 hours post dose.

A total of 20 (3×8 mL pre-dose and 17×6 mL post dose) blood samples were collected per subject after each dose. Pre-dose samples were collected at -1.00, -0.50, 0 hrs. Post dose samples were collected at 0.25, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 02.50, 3.00, 4.00, 6.00, 8.00, 12.00 24.00, 36.00 and 48.00 hours after dosing in vacutainers containing K₂EDTA. Based on an analysis of the collected blood samples, pharmacokinetic parameters including C_{max}, AUC_{0-t}, AUC_{0-∞}, and T_{max} were calculated using WinNonlin® version 5.3 (Pharsight Corporation). Although 72 patients were enrolled in the study, only data from the 62 patients who finished the study was used to calculate the values shown in Table 11, below.

TABLE 11

Mean Parameters (+/-SD)							
Treatments (Dose Dosage form, route) [Product ID]		C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (ng/mL) * hr	AUC _{0-∞} (ng/mL) * hr	t _{1/2} (hr)	K _{el} (hrs) ⁻¹
		Mean (% CV)	Median (Range)	Mean (% CV)	Mean (% CV)	Median (Range)	Mean (% CV)
Test product Progesterone Soft gel Capsule 200 mg. (Single dose) Oral	T	102.5744 ± 139.2924	03.00 (0.83-08.00)	145.9243 ± 166.3317	169.2228 ± 172.1370	3.9681 ± 3.6762	0.2994 ± 0.1827
Reference Product PROMETRIUM ® (Progesterone) soft gel Capsule 200 mg (Single dose- 2 × 200 mg), Oral	R ₁	83.8777 ± 142.4315	4.00 (01.00-12.00)	139.8621 ± 195.2669	159.2795 ± 204.2120	3.4829 ± 3.0843	0.3209 ± 0.1906
	R ₂	61.7121 ± 97.1097	4.00 (01.00-12.00)	98.6441 ± 130.9716	114.6482 ± 137.7684	3.4296 ± 2.9995	0.3485 ± 0.2491

Bioequivalence Analysis

In this study, the within-subject standard deviation of the reference formulation (S_{WR}) was found to be ≥0.294 for C_{max} and AUC (AUC_{0-t} and AUC_{0-∞}). As a result, the point estimate (test/reference geometric mean ratio) and 95% upper confidence bound for $(\mu_T/\mu_R)^2 \cdot (\theta S_{WR}^2)$ was determined using ln-transformed data using SAS® statistical software version 9.2 from SAS Institute Inc, USA. This methodology (Scaled-Average Bioequivalence ("SABE")) is consistent with FDA guidelines for calculating bioequivalence for highly variable drugs, such as progesterone. Using the SABE methodology, T demonstrated improved bioavail-

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ability compared to PROMETRIUM and was considered superior to PROMETRIUM. Supporting data is shown in Tables 12 and 13 below.

TABLE 12

Point of estimate, Within-subject SD (S_{wr}) and 95% Upper Confidence Bound of Test product (T) versus Reference product (R) for, Progesterone (Baseline corrected)

Parameter	Point Estimate (T/R ratio)	Within-Subject SD (S _{wr})	Upper 95% Confidence Bound
C _{max} (ng/mL)	1.38	1.1334	-0.481956
AUC _{0-t} (ng · hr/mL)	1.28	0.8908	-0.326613
AUC _{0-∞} (ng · hr/mL)	1.28	0.7704	-0.135158

TABLE 13

Point of estimate, Within-subject SD (S_{wr}) and 95% Upper Confidence Bound of Test product (T) versus Reference product (R) for, Progesterone (Baseline Uncorrected)

Parameter	Point of estimate (T/R ratio)	Within-subject SD (S _{wr})	95% Upper Confidence Bound
C _{max} (ng/mL)	1.38	1.1333729	-0.481836
AUC _{0-t} (ng · hr/mL)	1.28	0.8907574	-0.326277

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TABLE 13-continued

Point of estimate, Within-subject SD (S_{wr}) and 95% Upper Confidence Bound of Test product (T) versus Reference product (R) for, Progesterone (Baseline Uncorrected)

Parameter	Point of estimate (T/R ratio)	Within-subject SD (S _{wr})	95% Upper Confidence Bound
AUC _{0-∞} (ng · hr/mL)	1.29	0.7704431	-0.134134

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In view of the data noted above, the appropriate dosage of progesterone in the formulation disclosed herein necessary to achieve bioequivalence to PROMETRIUM was 150 mg. The computed results are shown in Table 14. This suggests that, in certain embodiments, the formulations disclosed herein have nearly 25% greater bioavailability than the current marketed formulation (PROMETRIUM).

TABLE 14

Summary of Evaluations of Baseline-Corrected Progesterone Results for a computed 150 mg Test Capsule vs. a 200 mg PROMETRIUM ® Capsule			
Parameter	Point Estimat	Within-Subject SD ($S_{w,r}$)	Upper 95% Confidence
C_{max} (ng/mL)	1.03	1.1334	-0.746836
AUC_{0-t} (ng · hr/mL)	0.96	0.8908	-0.465204

Example 16

Bioavailability Assessment—Fed #3

The amounts progesterone administered include 225 mg/day and 300 mg/day of progesterone. Progesterone capsule sizes are 75 mg and 150 mg capsules. Subjects taking the progesterone capsules are compared to subjects taking placebos. In both cases subjects are estrogen-primed.

The study includes: approximately a 6-week (42 days) screening period before enrolling into the study; approximately 6 weeks of Estrace®-priming before randomization; 6 weeks of blinded treatment (along with Estrace® treatment); and up to approximately 5 weeks of follow-up. The study is a phase 3, randomized, three-cycle, double-blind, placebo-controlled study to evaluate induction of secretory conversion of endometrium and withdrawal bleeding after administration of progesterone in estrogen-primed women with secondary amenorrhea. In clinical facilities, at the first visit (baseline—Cycle 1, day 1) subjects are estrogen-primed using an oral estradiol (i.e. 1.0 mg Estrace®). This priming takes place for 25 days. Compliance with estrogen-priming is determined (throughout, and at day 28-3 day to +1 day). Subjects will begin cycle 2 of estrogen-priming (Cycle 2, day 1).

After 12 days (± 2 days), subjects return to clinic. A transvaginal ultrasound (TVU) is conducted. Estrogen compliant subjects, and subjects meeting other criteria (i.e. double-walled endometrial thickness of ≥ 5 mm, $\geq 80\%$ compliant with Estrace®, and negative urine pregnancy test) are randomized for treatment with progesterone.

Subjects begin blinded administration on day 14 of Cycle 2. Subjects continue both Estrace® and blinded administration through day 25 of Cycle 2. No medication is taken from Cycle 2, Day 26-28.

Estrace® 1.0 mg is re-started at Cycle 3, Day 1 and continued until Day 25. Subjects will return to the clinic at Cycle 2, Day 12 (± 2 d) for study assessments. At Cycle 3, Day 14, subjects will again begin taking blinded study medication through Day 25.

Subjects return to the clinic day 24 (± 1 day) of Cycle 3, at which time an endometrial biopsy is conducted.

Subjects complete their final dose of Estrace® and blinded study medication on Day 25 and return to the clinic for a follow-up visit approximately 10 days later (upon receipt of biopsy results). Final visit assessments are con-

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ducted. Subjects whose endometrial biopsy results show proliferative endometrium are prescribed a 14 day course of medroxyprogesterone acetate 10 mg [MPA] as standard-of-care treatment to counterbalance the effect of estrogen-induced endometrial proliferation. These subjects receive a follow up telephone call at 2-4 weeks after completion of the MPA course and queried for the incidence of bleeding and adverse events. Unscheduled visits are allowed as needed.

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Example 17

An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study was conducted with progesterone soft gel capsules having the formulation disclosed in Table 9 as fill material and PROMETRIUM® soft gel capsule 200 mg in normal healthy, adult human male subjects under fasting conditions.

A total of 25 normal healthy, adult, human male subjects were enrolled into the study. All subjects were housed in the clinical facility for at least 11 hours before dosing through a 24 hours post dose. After an overnight fast of at least 10 hours, a single dose of either test product (T) or reference product (R) (as per a randomization schedule) was administered orally to each subject with 240 mL of water. There was a washout period of 14 days between treatments. 18 blood samples were collected at: -1 hours, -0.5 hours, 0 hours, 0.25 hours, 0.5 hours, 0.67 hours, 0.83 hours, 1.00 hours, 1.33 hours, 1.67 hours, 2.00 hours, 2.50 hours, 3.00 hours, 4.00 hours, 6.00 hours, 8.00 hours, 12.00 hours, and 24.00 hours. The testing indicated that T and R had the following PK parameters:

TABLE 15

Summary of Primary Pharmacokinetic Profile of Test product (T), Progesterone soft gel Capsule 200 mg (Baseline Corrected)			
Pharmacokinetic Parameter	Geometric Mean*	Arithmetic Mean	Standard Deviation
C_{max} (ng/mL)	0.9701	1.1767	1.7458
AUC_{0-t} (ng · hr/mL)	2.4130	4.5380	8.2350
$AUC_{0-\infty}$ (ng · hr/mL)	27.2091	36.9118	27.8580

*Estimate of Least Square Mean used to calculate Geometric Mean

TABLE 16

Summary of Primary Pharmacokinetic Profile of Reference product (R), PROMETRIUM ® (Progesterone) soft gel Capsule 200 mg (Baseline Corrected)			
Pharmacokinetic Parameter	Geometric Mean*	Arithmetic Mean	Standard Deviation
C_{max} (ng/mL)	2.0929	2.9877	3.1620
AUC_{0-t} (ng · hr/mL)	4.9870	7.6108	7.0148
$AUC_{0-\infty}$ (ng · hr/mL)	13.1050	26.8905	55.3784

*Estimate of Least Square Mean used to calculate Geometric Mean

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TABLE 17

T/R Ratio and 90% Confidence Intervals of Test product (T) versus Reference product (R) for, Progesterone (Baseline Corrected)		
Pharmacokinetic Parameter	T/R Ratio %	90% Confidence Intervals
C_{max} (ng/mL)	46.35%	34.3% to 62.63%
AUC_{0-t} (ng · hr/mL)	48.39%	25.84% to 90.62%
$AUC_{0-\infty}$ (ng · hr/mL)	207.62%	72.18% to 597.25%

This data indicates that T and R are not bioequivalent because the 90% confidence interval of the least square mean of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were 34.3% to 62.63%, 25.84% to 90.62%, and 72.18% to 597.25% respectively. They were thus not within the limit of 80.00% and 125.00% used by the FDA to demonstrate bioequivalence.

Example 18

An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study was conducted with progesterone soft gel capsules having the formulation disclosed in Table 9 as fill material and PROMETRIUM® soft gel capsule 200 mg in normal healthy, adult human male subjects under fed conditions.

A total of 25 normal healthy, adult, human male subjects were enrolled into the study. All subjects were housed in the clinical facility for at least 11 hours before dosing through a 24 hours post dose. After an overnight fast of at least 10 hours, a high fat, high calorie breakfast was served 30 minutes before administering a single dose of either test product (T) or reference product (R) (as per a randomization schedule). Capsules were given to each subject orally with 240 mL of water. There was a washout period of 14 days between treatments. 18 blood samples were collected at: -1 hours, -0.5 hours, 0 hours, 0.25 hours, 0.5 hours, 0.67 hours, 0.83 hours, 1.00 hours, 1.33 hours, 1.67 hours, 2.00 hours, 2.50 hours, 3.00 hours, 4.00 hours, 6.00 hours, 8.00 hours, 12.00 hours, and 24.00 hours. The testing indicated that T and R had the following PK parameters:

TABLE 18

Summary of Primary Pharmacokinetic Profile of Test product (T), Progesterone soft gel Capsule 200 mg (Baseline Corrected)			
Pharmacokinetic Parameter	Geometric Mean*	Arithmetic Mean	Standard Deviation
C_{max} (ng/mL)	20.8344	88.1233	165.6133
AUC_{0-t} (ng · hr/mL)	42.6781	124.7467	215.4315
$AUC_{0-\infty}$ (ng · hr/mL)	59.0419	150.9140	237.6730

*Estimate of Least Square Mean used to calculate Geometric Mean

TABLE 19

Summary of Primary Pharmacokinetic Profile of Reference product (R), PROMETRIUM® (Progesterone) soft gel Capsule 200 mg (Baseline Corrected)			
Pharmacokinetic Parameter	Geometric Mean*	Arithmetic Mean	Standard Deviation
C_{max} (ng/mL)	12.4661	41.5344	87.8350
AUC_{0-t} (ng · hr/mL)	29.9365	60.0080	105.0084
$AUC_{0-\infty}$ (ng · hr/mL)	36.9906	65.4258	109.0883

*Estimate of Least Square Mean used to calculate Geometric Mean

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TABLE 20

T/R Ratio and 90% Confidence Intervals of Test product (T) versus Reference product (R) for, Progesterone (Baseline Corrected)			
5	Pharmacokinetic Parameter	T/R Ratio %	90% Confidence Intervals
C_{max} (ng/mL)	167.13%	79.38% to 351.89%	
AUC_{0-t} (ng · hr/mL)	142.56%	85.01% to 239.08%	
$AUC_{0-\infty}$ (ng · hr/mL)	159.61%	103.59% to 245.94%	

This data indicates that T and R are not bioequivalent because the 90% confidence interval of the least square mean of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were 79.38% to 351.89%, 85.01% to 239.08%, and 103.59% to 245.94%. They were thus not within the limit of 80.00% and 125.00% used by the FDA to demonstrate bioequivalence. But importantly, and unlike the fasted study, the fed study demonstrated that test product T demonstrated enhanced oral bioavailability vs. PROMETRIUM®.

It will be apparent to those skilled in the art that various modifications and variations can be made in this disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that this disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices or methods. The disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad, general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

45 What is claimed is:

1. A pharmaceutical composition for orally administering progesterone to a subject in need thereof, the composition comprising:

50 *progesterone; a solubilizing agent; and lauroyl polyoxyl-32 glycerides;* wherein the solubilizing agent comprises predominantly caprylic fatty acid (C8) and capric fatty acid (C10) tri-esters of glycerol; and wherein the progesterone is present from about 20 to about 50 weight percent of the composition.

55 2. The pharmaceutical composition of claim 1, wherein the solubilizing agent further comprises a C₆-C₁₂ fatty acid mono-ester of glycerol.

3. The pharmaceutical composition of claim 2, wherein the solubilizing agent further comprises a C₆-C₁₂ fatty acid di-ester of glycerol.

60 4. The pharmaceutical composition of claim 1, wherein the amount of progesterone is from 25 mg to 200 mg.

65 5. The pharmaceutical composition of claim 1, wherein the amount of progesterone is 75 mg or 150 mg.

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6. The pharmaceutical composition of claim 1, wherein the progesterone includes solubilized progesterone and suspended progesterone.

7. The pharmaceutical composition of claim 1, wherein the composition is provided in a gelatin capsule.

8. The pharmaceutical composition of claim 1, wherein the composition has a total mass of less than 500 mg.

9. The pharmaceutical composition of claim 1, wherein the amount of progesterone comprises about 33% by weight of the composition; the solubilizing agent comprises about 65% by weight of the composition, the non-ionic surfactant comprises about 1.7% by weight of the composition.

10. The pharmaceutical composition of claim 1, wherein the amount of progesterone comprises about 33.33% by weight of the composition; the solubilizing agent comprises about 64.93% by weight of the composition, the non-ionic surfactant comprises about 1.67% by weight of the composition.

11. The pharmaceutical composition of claim 9, further comprising an antioxidant.

12. The pharmaceutical composition of claim 11, wherein the antioxidant is butylated hydroxyl toluene.

13. The pharmaceutical composition of claim 12, wherein the amount of progesterone is 200 mg.

14. The pharmaceutical composition of claim 12, wherein the amount of progesterone is 150 mg.

15. The pharmaceutical composition of claim 12, wherein the progesterone is ultra-micronized and has an X50 of less than or equal to 15 microns.

16. The pharmaceutical composition of claim 1, wherein the progesterone is ultra-micronized and has an X90 of less than or equal to 25 microns.

17. The pharmaceutical composition of claim 1, wherein the progesterone is the sole active ingredient in the composition.

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18. A pharmaceutical composition for orally administering progesterone to a subject in need thereof, the composition comprising:

5 progesterone;
a solubilizing agent; and
lauroyl polyoxyethyl-32 glycerides;
wherein the solubilizing agent comprises predominantly caprylic fatty acid (C8) and capric fatty acid (C10) tri-esters of glycerol; and
wherein the progesterone is present from about 20 to about 50 weight percent of the composition and wherein less than 6 percent of the progesterone is soluble in the solubilizing agent.

10 19. The pharmaceutical composition of claim 18, wherein more than 5 percent of the progesterone is soluble in the solubilizing agent.

15 20. A method of treating a progesterone-deficient state in a subject in need thereof, the method comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 1.

20 21. The method of claim 20, wherein the progesterone-deficient state is endometrial hyperplasia, secondary amenorrhea, preterm birth, shortened cervix, or another disease states or condition treated with supplemental progesterone.

25 22. The method of claim 21, wherein the progesterone-deficient state is secondary amenorrhea.

23. A method of treating a progesterone-deficient state in a subject in need thereof, the method comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 18.

30 24. The method of claim 23, wherein the progesterone-deficient state is endometrial hyperplasia, secondary amenorrhea, preterm birth, shortened cervix, or another disease states or condition treated with supplemental progesterone.

35 25. The method of claim 24, wherein the progesterone-deficient state is secondary amenorrhea.

* * * * *

EXHIBIT P



US011103513B2

(12) **United States Patent**
Bernick et al.

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(45) **Date of Patent:** *Aug. 31, 2021

- (54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**
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- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
This patent is subject to a terminal disclaimer.
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US 2020/0281938 A1 Sep. 10, 2020

3,755,575 A	8/1973	Berman
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopilin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	van der Vies
4,093,709 A	6/1978	Choi et al.
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong
4,237,885 A	12/1980	Wong et al.
4,310,510 A	1/1982	Sherman et al.
4,327,725 A	5/1982	Cortese et al.
4,372,951 A	2/1983	Vorys
4,384,096 A	5/1983	Sonnabend
4,393,871 A	7/1983	Vorhauer et al.
4,402,695 A	9/1983	Wong
4,423,151 A	12/1983	Baranczuk
4,449,980 A	5/1984	Millar et al.
4,610,687 A	9/1986	Fogwell
4,629,449 A	12/1986	Wong
4,732,763 A	3/1988	Beck et al.

(Continued)

FOREIGN PATENT DOCUMENTS

BR	H001367-9	7/2012
CA	2612380	12/2006

(Continued)

OTHER PUBLICATIONS

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)
Pachman et al., "Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions," International Journal of Women's Health, May 7, 2010.*
ACTIVELLA® (estradiol/ norethindrone acetate) prescribing information (Nov. 2017) FDA Label, 39 pages.
Center for Drug Evaluation and Research, Application No. NDA 19-781, Clinical Pharmacology and Biopharmaceutics Reviews, 1998, 59 pages, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/19781.cfm.

(Continued)

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See application file for complete search history.

(56) References Cited**U.S. PATENT DOCUMENTS**

1,967,351 A	1/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman

(57) ABSTRACT

Pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent comprising a medium chain (C6-C12) oil.

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(56)	References Cited				
U.S. PATENT DOCUMENTS					
4,738,957 A	4/1988	Laurent et al.	5,735,801 A	4/1998	Caillouette
4,756,907 A	7/1988	Beck et al.	5,739,176 A	4/1998	Dunn et al.
4,762,717 A	8/1988	Crowley, Jr.	5,744,463 A	4/1998	Bair
4,788,062 A	11/1988	Gale et al.	5,747,058 A	5/1998	Tipton et al.
4,816,257 A	3/1989	Buster et al.	5,762,614 A	6/1998	Caillouette
4,822,616 A	4/1989	Zimmermann et al.	5,770,176 A	6/1998	Nargessi
4,865,848 A	9/1989	Cheng et al.	5,770,219 A	6/1998	Chiang et al.
4,900,734 A	2/1990	Maxson et al.	5,770,220 A	6/1998	Meconi et al.
4,906,475 A	3/1990	Kim	5,770,227 A	6/1998	Dong et al.
4,942,158 A	7/1990	Sarpotdar et al.	5,776,495 A	7/1998	Duclos et al.
4,961,931 A	10/1990	Wong	5,780,044 A	7/1998	Yewey et al.
5,030,629 A	7/1991	Rajadhyaksha	5,780,050 A	7/1998	Jain et al.
5,043,331 A	8/1991	Hirvonen et al.	5,788,980 A	8/1998	Nabahi
5,059,426 A	10/1991	Chiang et al.	5,788,984 A	8/1998	Guenther et al.
5,064,654 A	11/1991	Berner et al.	5,789,442 A	8/1998	Garfield et al.
5,108,995 A	4/1992	Casper	5,811,416 A	9/1998	Chwalisz et al.
5,128,138 A	7/1992	Blank	5,811,547 A	9/1998	Nakamichi et al.
5,130,137 A	7/1992	Crowley, Jr.	5,814,329 A	9/1998	Shah
5,140,021 A	8/1992	Maxson et al.	5,820,878 A	10/1998	Hirano et al.
5,164,416 A	11/1992	Nagai et al.	5,827,200 A	10/1998	Caillouette
5,211,952 A	5/1993	Spicer et al.	5,840,327 A	11/1998	Gale et al.
5,252,334 A	10/1993	Chiang et al.	5,843,468 A	12/1998	Burkoth et al.
5,280,023 A	1/1994	Ehrlich et al.	5,843,979 A	12/1998	Wille et al.
5,288,496 A	2/1994	Lewis	5,858,394 A	1/1999	Lipp et al.
5,340,584 A	8/1994	Spicer et al.	5,863,552 A	1/1999	Yue
5,340,585 A	8/1994	Pike et al.	5,866,603 A	2/1999	Li et al.
5,340,586 A	8/1994	Pike et al.	5,869,084 A	2/1999	Paradissis et al.
5,362,497 A	11/1994	Yamada et al.	5,882,676 A	3/1999	Lee et al.
5,382,573 A	1/1995	Casper	5,885,612 A	3/1999	Meconi et al.
5,393,528 A	2/1995	Staab	5,888,533 A	3/1999	Dunn
5,393,529 A	2/1995	Hoffmann et al.	5,891,462 A	4/1999	Carrara
5,419,910 A	5/1995	Lewis	5,891,868 A	4/1999	Cummings et al.
5,453,279 A	9/1995	Lee et al.	5,898,038 A	4/1999	Yallampalli et al.
5,468,736 A	11/1995	Hodgen	5,902,603 A	5/1999	Chen et al.
5,474,783 A	12/1995	Miranda et al.	5,904,931 A	5/1999	Lipp et al.
5,480,776 A	1/1996	Dullien	5,906,830 A	5/1999	Farinas et al.
5,514,673 A	5/1996	Heckenmuller et al.	5,912,010 A	6/1999	Wille et al.
5,516,528 A	5/1996	Hughes et al.	5,916,176 A	6/1999	Caillouette
5,527,534 A	6/1996	Myhling	RE36,247 E	7/1999	Plunkett et al.
5,529,782 A	6/1996	Staab	5,919,477 A	7/1999	Bevan et al.
5,538,736 A	7/1996	Hoffmann et al.	5,922,349 A	7/1999	Elliesen et al.
5,543,150 A	8/1996	Bologna et al.	5,928,666 A	7/1999	Farinas et al.
5,547,948 A	8/1996	Barcomb	5,942,243 A	8/1999	Shah
5,556,635 A	9/1996	Istin et al.	5,942,531 A	8/1999	Diaz et al.
5,565,199 A	10/1996	Page et al.	5,952,000 A	9/1999	Venkateshwaran et al.
5,567,831 A	10/1996	Li	5,958,446 A	9/1999	Miranda et al.
5,569,652 A	10/1996	Beier et al.	5,962,445 A	10/1999	Stewart
5,580,572 A	12/1996	Mikler et al.	5,968,919 A	10/1999	Samour et al.
5,582,592 A	12/1996	Kendrick	5,972,372 A	10/1999	Saleh et al.
5,585,370 A	12/1996	Casper	5,985,311 A	11/1999	Cordes et al.
5,595,759 A	1/1997	Wright et al.	5,985,850 A	11/1999	Falk et al.
5,595,970 A	1/1997	Garfield et al.	5,985,861 A	11/1999	Levine et al.
5,605,702 A	2/1997	Teillaud et al.	5,989,568 A	11/1999	Breton et al.
5,607,691 A	3/1997	Hale et al.	5,993,856 A	11/1999	Ragavan et al.
5,607,693 A	3/1997	Bonte et al.	6,001,846 A	12/1999	Edwards et al.
5,609,617 A	3/1997	Shealy et al.	6,007,835 A	12/1999	Bon Lapillonne et al.
5,620,705 A	4/1997	Dong et al.	6,010,715 A	1/2000	Wick et al.
5,626,866 A	5/1997	Ebert et al.	6,013,276 A	1/2000	Math et al.
5,629,021 A	5/1997	Wright	6,022,562 A	2/2000	Autant et al.
5,633,011 A	5/1997	Dong et al.	6,024,974 A	2/2000	Li
5,633,242 A	5/1997	Oettel et al.	6,024,976 A	2/2000	Miranda et al.
5,639,743 A	6/1997	Kaswan et al.	6,028,057 A	2/2000	Burns
5,653,983 A	8/1997	Meybeck et al.	6,030,948 A	2/2000	Mann
5,656,286 A	8/1997	Miranda et al.	6,039,968 A	3/2000	Nabahi
5,660,839 A	8/1997	Allec et al.	6,040,340 A	3/2000	Chwalisz et al.
5,662,927 A	9/1997	Ehrlich et al.	6,056,972 A	5/2000	Hermsmeyer
5,663,160 A	9/1997	Meybeck et al.	6,060,077 A	5/2000	Meignant
5,676,968 A	10/1997	Lipp et al.	6,068,853 A	5/2000	Giannos et al.
5,677,292 A	10/1997	Li et al.	6,074,625 A	6/2000	Hawthorne et al.
5,686,097 A	11/1997	Taskovich et al.	6,077,531 A	6/2000	Salin-Drouin
5,693,335 A	12/1997	Xia et al.	6,080,118 A	6/2000	Blythe
5,694,947 A	12/1997	Lehtinen et al.	6,083,178 A	7/2000	Caillouette
5,700,480 A	12/1997	Hille et al.	6,086,916 A	7/2000	Agnus et al.
5,709,844 A	1/1998	Arbeit et al.	6,087,352 A	7/2000	Trout
5,719,197 A	2/1998	Kanios et al.	6,090,404 A	7/2000	Meconi et al.
			6,096,338 A	8/2000	Lacy et al.
			6,106,848 A	8/2000	Preuilh et al.
			6,117,446 A	9/2000	Place
			6,117,450 A	9/2000	Dittgen et al.

US 11,103,513 B2

Page 3

(56)	References Cited				
U.S. PATENT DOCUMENTS					
6,124,362 A	9/2000	Bradbury et al.	6,531,149 B1	3/2003	Kirstgen et al.
6,133,251 A	10/2000	Dittgen et al.	6,537,580 B1	3/2003	Savoir et al.
6,133,320 A	10/2000	Yallampalli et al.	6,538,039 B2	3/2003	Laurent
6,139,868 A	10/2000	Hoffmann	6,544,196 B2	4/2003	Caillouette
6,139,873 A	10/2000	Hughes, Jr. et al.	6,544,553 B1	4/2003	Hsia et al.
6,149,935 A	11/2000	Chiang et al.	6,548,053 B1	4/2003	Stewart et al.
6,153,216 A	11/2000	Cordes et al.	6,548,491 B2	4/2003	Tanabe et al.
6,165,491 A	12/2000	Grasset et al.	6,551,611 B2	4/2003	Elliesen et al.
6,165,975 A	12/2000	Adams et al.	6,555,131 B1	4/2003	Wolff et al.
6,187,323 B1	2/2001	Aiache et al.	6,562,367 B1	5/2003	Wolff et al.
6,187,339 B1	2/2001	de Haan et al.	6,562,370 B2	5/2003	Luo et al.
6,190,331 B1	2/2001	Caillouette	6,562,790 B2	5/2003	Chein
6,201,072 B1	3/2001	Rathi et al.	6,569,463 B2	5/2003	Patel et al.
6,217,886 B1	4/2001	Onyuksel et al.	6,583,129 B1	6/2003	Mazer et al.
6,225,297 B1	5/2001	Stockemann et al.	6,586,006 B2	7/2003	Roser et al.
6,227,202 B1	5/2001	Matapurkar	6,589,549 B2	7/2003	Shih et al.
6,228,383 B1	5/2001	Hansen et al.	6,593,317 B1	7/2003	de Ziegler et al.
6,228,852 B1	5/2001	Shaak	6,599,519 B1	7/2003	Seo et al.
6,242,509 B1	6/2001	Berger et al.	6,610,325 B1	8/2003	Meignant et al.
6,245,811 B1	6/2001	Horrobin et al.	6,610,652 B2	8/2003	Adams et al.
6,262,115 B1	7/2001	Guittard et al.	6,610,670 B2	8/2003	Blckensfeld et al.
6,267,984 B1	7/2001	Beste et al.	6,610,674 B1	8/2003	Schreiber
6,274,165 B1	8/2001	Meconi et al.	6,635,274 B1	10/2003	Masiz et al.
6,277,418 B1	8/2001	Marakverich et al.	6,638,528 B1	10/2003	Kanios
6,283,927 B1	9/2001	Caillouette	6,645,528 B1	10/2003	Savoir et al.
6,287,588 B1	9/2001	Shih et al.	6,649,155 B1	11/2003	Straub et al.
6,287,693 B1	9/2001	Savoir et al.	6,653,298 B2	11/2003	Dunlop et al.
6,291,527 B1	9/2001	Giorgetti	6,656,929 B1	11/2003	Potter et al.
6,294,188 B1	9/2001	Ragavan et al.	6,660,726 B2	12/2003	Agnus et al.
6,294,192 B1	9/2001	Patel et al.	6,663,608 B2	12/2003	Hill et al.
6,294,550 B1	9/2001	Place et al.	6,663,895 B2	12/2003	Rathbone et al.
6,299,900 B1	10/2001	Reed et al.	6,664,296 B1	12/2003	Meignant
6,303,132 B1	10/2001	Nelson	6,682,757 B1	1/2004	Wright
6,303,588 B1	10/2001	Danielov	6,692,763 B1	2/2004	Cummings et al.
6,306,841 B1	10/2001	Place et al.	6,708,822 B1	3/2004	Muni
6,306,914 B1	10/2001	de Ziegler et al.	6,716,454 B2	4/2004	Meignant et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,720,001 B2	4/2004	Chen et al.
6,309,848 B1	10/2001	Howett et al.	6,737,081 B2	5/2004	Savoir et al.
6,312,703 B1	11/2001	Orthofer	6,740,333 B2	5/2004	Beckett et al.
6,328,987 B1	12/2001	Marini	6,743,448 B2	6/2004	Kryger
6,342,491 B1	1/2002	Dey et al.	6,743,815 B2	6/2004	Huebner et al.
6,344,211 B1	2/2002	Hille et al.	6,747,018 B2	6/2004	Tanabe et al.
6,372,209 B1	4/2002	Chrisope	6,750,291 B2	6/2004	Kim et al.
6,372,245 B1	4/2002	Bowman et al.	6,756,208 B2	6/2004	Griffin et al.
6,372,246 B1	4/2002	Wei et al.	6,776,164 B2	8/2004	Bunt et al.
6,387,390 B1	5/2002	Deaver et al.	6,787,152 B2	9/2004	Kirby et al.
6,402,705 B1	6/2002	Caillorette	6,805,877 B2	10/2004	Massara et al.
6,416,778 B1	7/2002	Ragavant et al.	6,809,085 B1	10/2004	Elson et al.
6,420,352 B1	7/2002	Knowles	6,818,226 B2	11/2004	Reed et al.
6,423,039 B1	7/2002	Rathbone et al.	6,821,524 B2	11/2004	Marini
6,423,683 B1	7/2002	Heaton et al.	6,841,716 B1	1/2005	Tsutsumi
6,432,438 B1	8/2002	Shukla	6,844,334 B2	1/2005	Hill et al.
6,436,633 B1	8/2002	Kreider et al.	6,855,703 B1	2/2005	Hill et al.
6,440,454 B1	8/2002	Santoro et al.	6,860,859 B2	3/2005	Mehrotra et al.
6,444,224 B1	9/2002	Rathbone et al.	6,866,865 B2	3/2005	Hsia et al.
6,444,234 B1	9/2002	Kirby et al.	6,869,969 B2	3/2005	Huebner et al.
6,451,300 B1	9/2002	Dunlop et al.	6,878,518 B2	4/2005	Whitehead
6,451,339 B2	9/2002	Patel et al.	6,901,278 B1	5/2005	Notelovitz
6,451,779 B1	9/2002	Hesch	6,905,705 B2	6/2005	Palm et al.
6,455,246 B1	9/2002	Howett et al.	6,911,211 B2	6/2005	Eini et al.
6,455,517 B1	9/2002	Tanabe et al.	6,911,438 B2	6/2005	Wright
6,465,004 B1	10/2002	Rossi Montero et al.	6,923,988 B2	8/2005	Patel et al.
6,465,005 B1	10/2002	Biali et al.	6,924,274 B2	8/2005	Lardy et al.
6,465,006 B1	10/2002	Zhang et al.	6,932,983 B1	8/2005	Straub et al.
6,468,526 B2	10/2002	Chrisope	6,939,558 B2	9/2005	Massara et al.
6,469,016 B1	10/2002	Place et al.	6,943,021 B2	9/2005	Klausner et al.
6,472,434 B1	10/2002	Place et al.	6,958,327 B1	10/2005	Hillisch et al.
6,479,232 B1	11/2002	Howett et al.	6,960,337 B2	11/2005	Daniels et al.
6,495,160 B2	12/2002	Esposito et al.	6,962,691 B1	11/2005	Lulla et al.
6,500,814 B1	12/2002	Hesch	6,962,908 B2	11/2005	Aloba et al.
6,503,896 B1	1/2003	Tanabe et al.	6,967,194 B1	11/2005	Matsuo et al.
6,511,969 B1	1/2003	Hermsmeyer	6,974,569 B2	12/2005	Dunlop et al.
6,521,250 B2	2/2003	Meconi et al.	6,977,250 B2	12/2005	Rodriguez
6,526,980 B1	3/2003	Tracy et al.	6,978,945 B2	12/2005	Wong et al.
6,528,094 B1	3/2003	Savoir et al.	6,987,129 B2	1/2006	Mak et al.

US 11,103,513 B2

Page 4

(56)	References Cited				
U.S. PATENT DOCUMENTS					
7,011,846 B2	3/2006 Shojaei et al.	7,862,552 B2	1/2011 McIntyre et al.		
7,018,992 B2	3/2006 Koch et al.	7,867,990 B2	1/2011 Schultz et al.		
7,030,104 B2	4/2006 Gray et al.	7,871,643 B2	1/2011 Lizio et al.		
7,030,157 B2	4/2006 Ke et al.	7,879,830 B2	2/2011 Wiley		
RE39,104 E	5/2006 Duclos et al.	7,884,093 B2	2/2011 Creasy et al.		
7,074,779 B2	7/2006 Sui et al.	7,925,519 B2	4/2011 Greene		
7,083,590 B1	8/2006 Bunt et al.	7,939,104 B2	5/2011 Barbera et al.		
7,091,213 B2	8/2006 Metcalf, III et al.	7,943,602 B2	5/2011 Bunschoten et al.		
7,094,228 B2	8/2006 Zhang et al.	7,943,604 B2	5/2011 Coelingh Bennink et al.		
7,097,853 B1	8/2006 Garbe et al.	7,945,459 B2	5/2011 Grace et al.		
7,101,342 B1	9/2006 Caillouette	7,960,368 B2	6/2011 Nickisch et al.		
7,105,573 B2	9/2006 Krajcik et al.	7,989,436 B2	8/2011 Hill et al.		
7,135,190 B2	11/2006 Piao et al.	7,989,487 B2	8/2011 Welsh et al.		
7,153,522 B1	12/2006 Ikeura et al.	8,022,053 B2	9/2011 Mueller et al.		
7,163,681 B2	1/2007 Giles-Komar et al.	8,048,017 B2	11/2011 Xu		
7,163,699 B2	1/2007 Besse	8,048,869 B2	11/2011 Bunschoten et al.		
7,175,850 B2	2/2007 Cevc	8,063,030 B2	11/2011 Ellman		
7,179,799 B2	2/2007 Hill et al.	8,071,576 B2	12/2011 Coelingh Bennink et al.		
7,196,074 B2	3/2007 Blye et al.	8,071,729 B2	12/2011 Giles-Komar et al.		
7,198,800 B1	4/2007 Ko	8,075,916 B2	12/2011 Song et al.		
7,198,801 B2	4/2007 Carrara et al.	8,075,917 B2	12/2011 Chung et al.		
7,226,910 B2	6/2007 Wilson et al.	8,076,317 B2	12/2011 Kulmann		
7,247,625 B2	7/2007 Zhang et al.	8,076,319 B2	12/2011 Leonard		
7,250,446 B2	7/2007 Sangita et al.	8,080,553 B2	12/2011 Keith et al.		
7,267,829 B2	9/2007 Kirby et al.	8,088,605 B2	1/2012 Beaudet et al.		
7,300,926 B2	11/2007 Prokai et al.	8,096,940 B2	1/2012 Josephson et al.		
7,303,763 B2	12/2007 Ho	8,101,209 B2	1/2012 Legrand et al.		
7,317,037 B2	1/2008 Fensome et al.	8,101,773 B2	1/2012 Smith et al.		
7,329,654 B2	2/2008 Kanojia et al.	8,114,152 B2	2/2012 Furst		
7,335,650 B2	2/2008 Potter et al.	8,114,434 B2	2/2012 Sasaki et al.		
7,374,779 B2	5/2008 Chen et al.	8,114,442 B2	2/2012 Tucker et al.		
7,378,404 B2	5/2008 Peters et al.	8,119,741 B2	2/2012 Pavlin		
7,381,427 B2	6/2008 Ancira et al.	8,121,886 B2	2/2012 Azar		
7,387,789 B2	6/2008 Klose et al.	8,124,118 B2	2/2012 Lennernas et al.		
7,388,006 B2	6/2008 Schmees et al.	8,124,595 B2	2/2012 Boissonneault		
7,414,043 B2	8/2008 Kosemund et al.	8,147,561 B2	4/2012 Binmoeller		
7,427,413 B2	9/2008 Savoie et al.	8,148,546 B2	4/2012 Schuster et al.		
7,427,609 B2	9/2008 Leonard	8,158,613 B2	4/2012 Staniforth et al.		
7,429,576 B2	9/2008 Labrie	8,158,614 B2	4/2012 Lambert et al.		
7,431,941 B2	10/2008 Besins et al.	8,163,722 B2	4/2012 Savoie et al.		
7,456,159 B2	11/2008 Houze et al.	8,177,449 B2	5/2012 Bayly et al.		
7,459,445 B2	12/2008 Hill et al.	8,182,833 B2	5/2012 Hermsmeyer		
7,465,587 B2	12/2008 Imrich	8,187,615 B2	5/2012 Friedman		
7,470,433 B2	12/2008 Carrara et al.	8,187,640 B2	5/2012 Dunn		
7,485,666 B2	2/2009 Villanueva et al.	8,195,403 B2	6/2012 Ishikawa et al.		
7,497,855 B2	3/2009 Ausiello et al.	8,202,736 B2	6/2012 Mousa et al.		
7,498,303 B2	3/2009 Arnold et al.	8,217,024 B2	7/2012 Ahmed et al.		
7,534,765 B2	5/2009 Gregg et al.	8,221,785 B2	7/2012 Chien		
7,534,780 B2	5/2009 Wyrwa et al.	8,222,008 B2	7/2012 Thoene		
7,550,142 B2	6/2009 Giles-Komar et al.	8,222,237 B2	7/2012 Nickisch et al.		
7,563,565 B1	7/2009 Matsuo et al.	8,227,454 B2	7/2012 Hill et al.		
7,569,274 B2	8/2009 Besse et al.	8,227,509 B2	7/2012 Castro et al.		
7,572,779 B2	8/2009 Aloba et al.	8,241,664 B2	8/2012 Dudley et al.		
7,572,780 B2	8/2009 Hermsmeyer	8,247,393 B2	8/2012 Ahmed et al.		
7,589,082 B2	9/2009 Savoie et al.	8,257,724 B2	9/2012 Cromack et al.		
7,671,027 B2	3/2010 Loumaye	8,257,725 B2	9/2012 Cromack et al.		
7,674,783 B2	3/2010 Hermsmeyer	8,268,352 B2	9/2012 Vaya et al.		
7,687,281 B2	3/2010 Roth et al.	8,268,806 B2	9/2012 Labrie		
7,687,485 B2	3/2010 Levinson et al.	8,268,878 B2	9/2012 Armer et al.		
7,694,683 B2	4/2010 Callister et al.	8,273,730 B2	9/2012 Fernandez et al.		
7,704,983 B1	4/2010 Hodgen et al.	8,287,888 B2	10/2012 Song et al.		
7,727,720 B2	6/2010 Dhallan	8,288,366 B2	10/2012 Chochinov et al.		
7,732,408 B2	6/2010 Josephson et al.	8,318,898 B2	11/2012 Fasel et al.		
7,749,989 B2	7/2010 Hill et al.	8,324,193 B2	12/2012 Lee Sepsick et al.		
7,767,656 B2	8/2010 Shoichet et al.	8,329,680 B2	12/2012 Evans et al.		
7,799,769 B2	9/2010 White et al.	8,337,814 B2	12/2012 Osbakken et al.		
7,815,936 B2	10/2010 Hasenzahl et al.	8,344,007 B2	1/2013 Tang et al.		
7,815,949 B2	10/2010 Cohen	8,349,820 B2	1/2013 Zeun et al.		
7,829,115 B2	11/2010 Besins et al.	8,353,863 B2	1/2013 Imran		
7,829,116 B2	11/2010 Griswold et al.	8,357,723 B2	1/2013 Satyam		
RE42,012 E	12/2010 Deaver et al.	8,361,995 B2	1/2013 Schramm		
7,850,992 B2	12/2010 Kim et al.	8,362,091 B2	1/2013 Tamarkin et al.		
7,854,753 B2	12/2010 Kraft et al.	8,372,424 B2	2/2013 Berry et al.		
7,858,607 B2	12/2010 Mamchur	8,372,806 B2	2/2013 Boehler et al.		
RE42,072 E	1/2011 Deaver et al.	8,377,482 B2	2/2013 Laurie et al.		
		8,377,994 B2	2/2013 Gray et al.		
		8,394,759 B2	3/2013 Barathur et al.		
		8,415,332 B2	4/2013 Diliberti et al.		
		8,420,111 B2	4/2013 Hermsmeyer		

US 11,103,513 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
8,435,561 B2	5/2013	Besins et al.	10,568,891 B2	2/2020	Mirkin et al.	
8,435,972 B2	5/2013	Stein et al.	10,668,082 B2	6/2020	Mirkin et al.	
8,449,879 B2	5/2013	Laurent Applegate et al.	10,675,288 B2	6/2020	Bernick et al.	
8,450,108 B2	5/2013	Boyce	10,806,697 B2	10/2020	Bernick et al.	
8,454,945 B2	6/2013	McCook et al.	10,806,740 B2	10/2020	Persicaner et al.	
8,455,468 B2	6/2013	Hoffman et al.	10,835,487 B2	11/2020	Bernick et al.	
8,461,138 B2	6/2013	Boissonneault	10,888,516 B2	1/2021	Bernick et al.	
8,476,252 B2	7/2013	Achleitner et al.	2001/0005728 A1	6/2001	Guittard et al.	
8,481,488 B2	7/2013	Carter	2001/0009673 A1	7/2001	Lipp et al.	
8,486,374 B2	7/2013	Tamarkin et al.	2001/0021816 A1	9/2001	Caillouette	
8,486,442 B2	7/2013	Matsushita et al.	2001/0023261 A1	9/2001	Ryoo et al.	
8,492,368 B2	7/2013	Vanlandingham et al.	2001/0027189 A1	10/2001	Bennink et al.	
8,507,467 B2	8/2013	Matsui et al.	2001/0029357 A1	10/2001	Bunt et al.	
8,512,693 B2	8/2013	Capito et al.	2001/0031747 A1	10/2001	de Ziegler et al.	
8,512,754 B2	8/2013	Needham	2001/0032125 A1	10/2001	Bhan et al.	
8,518,376 B2	8/2013	Tamarkin et al.	2001/0034340 A1	10/2001	Pickar	
8,536,159 B2	9/2013	Li et al.	2001/0053383 A1	12/2001	Miranda et al.	
8,540,967 B2	9/2013	Barrett et al.	2001/0056068 A1	12/2001	Chwalisz et al.	
8,541,400 B2	9/2013	Johnsson et al.	2002/0012710 A1	1/2002	Lansky	
8,551,462 B2	10/2013	Goldstein et al.	2002/0026158 A1	2/2002	Rathbone et al.	
8,551,508 B2	10/2013	Lee et al.	2002/0028788 A1	3/2002	Bunt et al.	
8,557,281 B2	10/2013	Halliday et al.	2002/0035070 A1	3/2002	Gardlik et al.	
8,568,374 B2	10/2013	De Graaf et al.	2002/0058648 A1	5/2002	Hammerly	
8,591,951 B2	11/2013	Kohn et al.	2002/0058926 A1	5/2002	Rathbone et al.	
8,613,951 B2	12/2013	Zale et al.	2002/0064541 A1	5/2002	Lapidot et al.	
8,633,178 B2	1/2014	Bernick et al.	2002/0076441 A1	6/2002	Shih et al.	
8,633,180 B2	1/2014	Li et al.	2002/0102308 A1	8/2002	Wei et al.	
8,636,787 B2	1/2014	Sabaria	2002/0107230 A1	8/2002	Waldon et al.	
8,636,982 B2	1/2014	Tamarkin et al.	2002/0114803 A1	8/2002	Deaver et al.	
8,653,129 B2	2/2014	Fein et al.	2002/0119174 A1	8/2002	Gardlik et al.	
8,658,627 B2	2/2014	Voskuhl	2002/0119198 A1	8/2002	Gao et al.	
8,658,628 B2	2/2014	Baucom	2002/0132801 A1	9/2002	Heil et al.	
8,663,681 B2	3/2014	Ahmed et al.	2002/0137749 A1	9/2002	Levinson et al.	
8,663,692 B1	3/2014	Mueller et al.	2002/0142017 A1	10/2002	Simonnet	
8,663,703 B2	3/2014	Lerner et al.	2002/0151530 A1	10/2002	Leonard et al.	
8,664,207 B2	3/2014	Li et al.	2002/0156394 A1	10/2002	Mehrotra et al.	
8,669,293 B2	3/2014	Levy et al.	2002/0169150 A1	11/2002	Pickar	
8,679,552 B2	3/2014	Guthery	2002/0169205 A1	11/2002	Chwalisz et al.	
8,694,358 B2	4/2014	Tryfon	2002/0173510 A1	11/2002	Levinson et al.	
8,697,127 B2	4/2014	Sah	2002/0193356 A1	12/2002	Van Beek et al.	
8,697,710 B2	4/2014	Li et al.	2002/0193758 A1	12/2002	Sandberg	
8,703,105 B2	4/2014	Tamarkin et al.	2002/0197286 A1	12/2002	Brandman et al.	
8,709,385 B2	4/2014	Tamarkin et al.	2003/0003139 A1	1/2003	Lipp et al.	
8,709,451 B2	4/2014	Nam et al.	2003/0004145 A1	1/2003	Leonard	
8,715,735 B2	5/2014	Funk et al.	2003/0007994 A1	1/2003	Bunt et al.	
8,721,331 B2	5/2014	Raghuprasad	2003/0027772 A1	2/2003	Breton	
8,722,021 B2	5/2014	Friedman et al.	2003/0044453 A1	3/2003	Dittgen et al.	
8,734,846 B2	5/2014	Ali et al.	2003/0049307 A1	3/2003	Gynrik	
8,735,381 B2	5/2014	Podolski	2003/0064097 A1	4/2003	Patel et al.	
8,741,336 B2	6/2014	Dipierro et al.	2003/0064975 A1	4/2003	Koch et al.	
8,741,373 B2	6/2014	Bromley et al.	2003/0072760 A1	4/2003	Sirbasku	
8,753,661 B2	6/2014	Steinmuller et al.	2003/0073248 A1	4/2003	Roth et al.	
8,784,882 B2	7/2014	Mattern	2003/0073673 A1	4/2003	Hesch	
8,846,648 B2	9/2014	Bernick et al.	2003/0077297 A1 *	4/2003	Chen	A61K 9/4808
8,846,649 B2	9/2014	Bernick et al.		424/400		
8,933,059 B2	1/2015	Bernick et al.	2003/0078245 A1	4/2003	Bennink et al.	
8,987,237 B2	3/2015	Bernick et al.	2003/0091620 A1	5/2003	Fikstad et al.	
8,987,238 B2	3/2015	Bernick et al.	2003/0091640 A1	5/2003	Ramanathan et al.	
8,993,548 B2	3/2015	Bernick et al.	2003/0092691 A1	5/2003	Besse et al.	
8,993,549 B2	3/2015	Bernick et al.	2003/0096012 A1	5/2003	Besse et al.	
9,006,222 B2	4/2015	Bernick et al.	2003/0104048 A1	6/2003	Patel et al.	
9,012,434 B2	4/2015	Bernick et al.	2003/0109507 A1	6/2003	Franke et al.	
9,114,145 B2	8/2015	Bernick et al.	2003/0113268 A1	6/2003	Buenafae et al.	
9,114,146 B2	8/2015	Bernick et al.	2003/0114420 A1	6/2003	Salvati et al.	
9,180,091 B2	11/2015	Bernick et al.	2003/0114430 A1	6/2003	MacLeod et al.	
9,248,136 B2	2/2016	Bernick et al.	2003/0124182 A1	7/2003	Shojaei et al.	
9,289,382 B2	3/2016	Bernick et al.	2003/0124191 A1	7/2003	Besse et al.	
9,301,920 B2	4/2016	Bernick et al.	2003/0130558 A1	7/2003	Massara et al.	
10,052,386 B2	8/2018	Bernick et al.	2003/0144258 A1	7/2003	Heil et al.	
10,098,894 B2	10/2018	Amadio et al.	2003/0157157 A1	8/2003	Luo et al.	
10,206,932 B2	2/2019	Bernick et al.	2003/0166509 A1	9/2003	Edwards et al.	
10,258,630 B2	4/2019	Mirkin et al.	2003/0170295 A1	9/2003	Kim et al.	
10,398,708 B2	9/2019	Mirkin et al.	2003/0175329 A1	9/2003	Azarnoff et al.	
10,471,072 B2	11/2019	Bernick et al.	2003/0175333 A1	9/2003	Shefer et al.	
10,537,581 B2	1/2020	Bernick et al.	2003/0180352 A1	9/2003	Patel et al.	
			2003/0181353 A1	9/2003	Nyce	
			2003/0181728 A1	9/2003	Salvati et al.	
			2003/0191096 A1	10/2003	Leonard et al.	
			2003/0195177 A1	10/2003	Leonard et al.	

US 11,103,513 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2003/0215496 A1	11/2003	Patel et al.	2005/0118244 A1	6/2005	Theobild et al.
2003/0219402 A1	11/2003	Rutter	2005/0118272 A1	6/2005	Besse et al.
2003/0220297 A1	11/2003	Bernstein et al.	2005/0129756 A1	6/2005	Podhaisky et al.
2003/0224057 A1	12/2003	Martin-Letellier et al.	2005/0152956 A1	7/2005	Dudley
2003/0224059 A1	12/2003	Lerner et al.	2005/0153946 A1	7/2005	Hirsh et al.
2003/0225047 A1	12/2003	Caubel et al.	2005/0164977 A1	7/2005	Coelingh Bennink
2003/0225048 A1	12/2003	Caubel et al.	2005/0182105 A1	8/2005	Nirschl et al.
2003/0225050 A1	12/2003	Eichardt et al.	2005/0186141 A1	8/2005	Gonda et al.
2003/0228686 A1	12/2003	Klausner et al.	2005/0187267 A1	8/2005	Hamann et al.
2003/0229057 A1	12/2003	Caubel et al.	2005/0192253 A1	9/2005	Salvati et al.
2003/0235596 A1	12/2003	Gao et al.	2005/0192310 A1	9/2005	Gavai et al.
2003/0236236 A1	12/2003	Chen et al.	2005/0196434 A1	9/2005	Briere
2004/0009960 A1	1/2004	Heil et al.	2005/0207990 A1	9/2005	Funke et al.
2004/0022820 A1	2/2004	Anderson	2005/0209209 A1	9/2005	Koch et al.
2004/0034001 A1	2/2004	Karara	2005/0214384 A1	9/2005	Juturu et al.
2004/0037881 A1	2/2004	Guittard et al.	2005/0220825 A1	10/2005	Funke et al.
2004/0039356 A1	2/2004	Maki et al.	2005/0220900 A1	10/2005	Popp et al.
2004/0043043 A1	3/2004	Schlyter et al.	2005/0222106 A1	10/2005	Bracht
2004/0043943 A1	3/2004	Guittard et al.	2005/0228692 A1	10/2005	Hodgdon
2004/0044080 A1	3/2004	Place et al.	2005/0228718 A1	10/2005	Austin
2004/0048900 A1	3/2004	Flood	2005/0239747 A1	10/2005	Yang et al.
2004/0052824 A1	3/2004	Abou Chakra-Vernet et al.	2005/0239758 A1	10/2005	Roby
2004/0073024 A1	4/2004	Metcalf, III et al.	2005/0244360 A1	11/2005	Billoni
2004/0077605 A1	4/2004	Salvati et al.	2005/0244522 A1	11/2005	Canara et al.
2004/0077606 A1	4/2004	Salvati et al.	2005/0245902 A1	11/2005	Cornish et al.
2004/0087548 A1	5/2004	Salvati et al.	2005/0250746 A1	11/2005	Iammateo
2004/0087564 A1	5/2004	Wright et al.	2005/0250750 A1	11/2005	Cummings et al.
2004/0089308 A1	5/2004	Welch	2005/0250753 A1	11/2005	Fink et al.
2004/0092494 A9	5/2004	Dudley	2005/0256028 A1	11/2005	Yun et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0266078 A1	12/2005	Jorda et al.
2004/0093261 A1	5/2004	Jain et al.	2005/0266088 A1	12/2005	Hinrichs et al.
2004/0097468 A1	5/2004	Wimalawansa	2005/0271597 A1	12/2005	Keith
2004/0101557 A1	5/2004	Gibson et al.	2005/0271598 A1	12/2005	Friedman et al.
2004/0106542 A1	6/2004	Deaver et al.	2005/0272685 A1	12/2005	Hung
2004/0110732 A1	6/2004	Masini Eteve et al.	2005/0272712 A1	12/2005	Grubb et al.
2004/0131670 A1	7/2004	Gao	2006/0009428 A1	1/2006	Grubb et al.
2004/0138103 A1	7/2004	Patt	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0142012 A1	7/2004	Bunt et al.	2006/0018937 A1	1/2006	Friedman et al.
2004/0146539 A1	7/2004	Gupta	2006/0019978 A1	1/2006	Balog
2004/0146894 A1	7/2004	Warrington et al.	2006/0020002 A1	1/2006	Salvati et al.
2004/0147578 A1	7/2004	Calvet	2006/0030615 A1	2/2006	Fensome et al.
2004/0161435 A1	8/2004	Gupta	2006/0034889 A1	2/2006	Jo et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0034904 A1	2/2006	Weimann
2004/0176336 A1	9/2004	Rodriguez	2006/0040904 A1	2/2006	Ahmed et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0052341 A1	3/2006	Cornish et al.
2004/0191276 A1	9/2004	Muni	2006/0069031 A1	3/2006	Loumaye
2004/0198706 A1	10/2004	Carrara et al.	2006/0078618 A1	4/2006	Constantinides et al.
2004/0210280 A1	10/2004	Liedtke	2006/0083778 A1	4/2006	Allison et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0084704 A1	4/2006	Shih et al.
2004/0219124 A1	11/2004	Gupta	2006/0088580 A1	4/2006	Meconi et al.
2004/0225140 A1	11/2004	Fernandez et al.	2006/0089337 A1	4/2006	Casper et al.
2004/0234606 A1	11/2004	Levine et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0241219 A1	12/2004	Hille et al.	2006/0100180 A1	5/2006	Nubbemeyer et al.
2004/0243437 A1	12/2004	Grace et al.	2006/0106004 A1	5/2006	Brody et al.
2004/0253319 A1	12/2004	Netke et al.	2006/0110415 A1	5/2006	Gupta
2004/0259817 A1	12/2004	Waldon et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0121102 A1	6/2006	Chiang
2005/0003003 A1	1/2005	Bisu et al.	2006/0121626 A1	6/2006	Imrich
2005/0004088 A1	1/2005	Hesch	2006/0134188 A1	6/2006	Podhaisky et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2006/0135619 A1	6/2006	Kick et al.
2005/0014729 A1	1/2005	Pulaski	2006/0165744 A1	7/2006	Jamil et al.
2005/0020550 A1	1/2005	Morris et al.	2006/0193789 A1	8/2006	Tamarkin et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2006/0194775 A1	8/2006	Tofovic et al.
2005/0021009 A1	1/2005	Massara et al.	2006/0204557 A1	9/2006	Gupta et al.
2005/0025833 A1	2/2005	Aschkenasy et al.	2006/0233743 A1	10/2006	Kelly
2005/0031651 A1	2/2005	Gervais et al.	2006/0233841 A1	10/2006	Brodbeck et al.
2005/0042173 A1	2/2005	Besse et al.	2006/0235037 A1	10/2006	Purandare et al.
2005/0042268 A1	2/2005	Aschkenasy et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0048116 A1	3/2005	Straub et al.	2006/0246122 A1	11/2006	Langguth et al.
2005/0054991 A1	3/2005	Tobyn et al.	2006/0247216 A1	11/2006	Haj-Yehia
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0247221 A1	11/2006	Coelingh Bennink et al.
2005/0085453 A1	4/2005	Govindarajan	2006/0251581 A1	11/2006	McIntyre et al.
2005/0101579 A1	5/2005	Shippen	2006/0252049 A1	11/2006	Shuler et al.
2005/0113350 A1	5/2005	Duesterberg et al.	2006/0257472 A1	11/2006	Nielsen
			2006/0275218 A1	12/2006	Tamarkin et al.
			2006/0275360 A1	12/2006	Ahmed et al.
			2006/0276414 A1	12/2006	Coelingh Bennink et al.
			2006/0280771 A1	12/2006	Groenewegen et al.

US 11,103,513 B2

Page 7

(56)

References Cited**U.S. PATENT DOCUMENTS**

2006/0280797 A1	12/2006	Shoichet et al.	2008/0139392 A1	6/2008	Acosta Zara et al.
2006/0280800 A1	12/2006	Nagi et al.	2008/0145423 A1	6/2008	Khan et al.
2006/0292223 A1	12/2006	Woolfson et al.	2008/0153789 A1	6/2008	Dmowski et al.
2007/0004693 A1	1/2007	Woolfson et al.	2008/0175814 A1	7/2008	Phasivongsa et al.
2007/0004694 A1	1/2007	Woolfson et al.	2008/0175905 A1	7/2008	Liu et al.
2007/0009559 A1	1/2007	Li et al.	2008/0175908 A1	7/2008	Liu et al.
2007/0009594 A1	1/2007	Grubb et al.	2008/0188829 A1	8/2008	Creasy
2007/0010550 A1	1/2007	McKenzie	2008/0206156 A1	8/2008	Cronk
2007/0014839 A1	1/2007	Bracht	2008/0206159 A1	8/2008	Tamarkin et al.
2007/0015698 A1	1/2007	Kleinman et al.	2008/0206161 A1	8/2008	Tamarkin et al.
2007/0021360 A1	1/2007	Nyce et al.	2008/0214512 A1	9/2008	Seitz et al.
2007/0027201 A1	2/2007	McComas et al.	2008/0220069 A1	9/2008	Allison
2007/0031491 A1	2/2007	Levine et al.	2008/0226698 A1	9/2008	Tang et al.
2007/0037780 A1	2/2007	Ebert et al.	2008/0227763 A1	9/2008	Lanquetin
2007/0037782 A1	2/2007	Hibino et al.	2008/0234199 A1	9/2008	Katamreddy
2007/0042038 A1	2/2007	Besse	2008/0234240 A1	9/2008	Duesterberg et al.
2007/0060589 A1	3/2007	Purandare et al.	2008/0255078 A1	10/2008	Katamreddy
2007/0066628 A1	3/2007	Zhang et al.	2008/0255089 A1	10/2008	Katamrecidy
2007/0066637 A1	3/2007	Zhang et al.	2008/0261931 A1	10/2008	Hedner et al.
2007/0066675 A1	3/2007	Zhang et al.	2008/0299220 A1	12/2008	Tamarkin et al.
2007/0071777 A1	3/2007	Bromer et al.	2008/0306036 A1	12/2008	Katamreddy
2007/0078091 A1	4/2007	Hubler et al.	2008/0312197 A1	12/2008	Rodriguez
2007/0088029 A1	4/2007	Balog et al.	2008/0312198 A1	12/2008	Rodriguez
2007/0093548 A1	4/2007	Diffendal et al.	2008/0319078 A1	12/2008	Katamreddy
2007/0116729 A1	5/2007	Palepu	2009/0004246 A1	1/2009	Woolfson et al.
2007/0116829 A1	5/2007	Prakash et al.	2009/0010968 A1	1/2009	Allart et al.
2007/0128263 A1	6/2007	Gargiulo et al.	2009/0011041 A1	1/2009	Musaeva et al.
2007/0154533 A1	7/2007	Dudley	2009/0017120 A1	1/2009	Trimble et al.
2007/0167418 A1	7/2007	Ferguson	2009/0022683 A1	1/2009	Song et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0053294 A1	2/2009	Prendergast
2007/0185068 A1	8/2007	Ferguson et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0190022 A1	8/2007	Bicopoulos et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0191319 A1	8/2007	Ke et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196415 A1	8/2007	Chen et al.	2009/0074859 A1	3/2009	Patel
2007/0196433 A1	8/2007	Ron et al.	2009/0081206 A1	3/2009	Leibovitz
2007/0207225 A1	9/2007	Squadrito	2009/0081278 A1	3/2009	De Graaff et al.
2007/0225281 A1	9/2007	Zhang et al.	2009/0081303 A1	3/2009	Savoir et al.
2007/0232574 A1	10/2007	Galey et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0093440 A1	4/2009	Murad
2007/0243229 A1	10/2007	Smith et al.	2009/0098069 A1	4/2009	Vacca
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0099106 A1	4/2009	Phasivongsa et al.
2007/0254858 A1	11/2007	Cronk	2009/0099149 A1	4/2009	Liu et al.
2007/0255197 A1	11/2007	Humberstone et al.	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0264309 A1	11/2007	Chollet et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0264345 A1	11/2007	Eros et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0264349 A1	11/2007	Lee et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0286819 A1	12/2007	DeVries et al.	2009/0143344 A1	6/2009	Chang
2007/0287688 A1	12/2007	Chan et al.	2009/0164341 A1	6/2009	Sunvold et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0292359 A1	12/2007	Friedman et al.	2009/0181088 A1	7/2009	Song et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0186081 A1	7/2009	Holm et al.
2007/0292461 A1	12/2007	Tamarkin et al.	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0292493 A1	12/2007	Briere	2009/0203658 A1	8/2009	Marx et al.
2007/0298089 A1	12/2007	Saeki et al.	2009/0214474 A1	8/2009	Jennings
2008/0026035 A1	1/2008	Chollet et al.	2009/0227025 A1	9/2009	Nichols et al.
2008/0026040 A1	1/2008	Farr et al.	2009/0227550 A1	9/2009	Mattern
2008/0026062 A1	1/2008	Farr et al.	2009/0232897 A1	9/2009	Sahoo et al.
2008/0038219 A1	2/2008	Mosbiugh et al.	2009/0258096 A1	10/2009	Cohen
2008/0038350 A1	2/2008	Gerecke et al.	2009/0264395 A1	10/2009	Creasy
2008/0039405 A1	2/2008	Langley et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0050317 A1	2/2008	Tamarkin et al.	2009/0285772 A1	11/2009	Phasivongsa et al.
2008/0051351 A1	2/2008	Ghisalberti	2009/0285869 A1	11/2009	Trimble
2008/0063607 A1	3/2008	Tamarkin et al.	2009/0318558 A1	12/2009	Kim et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2009/0324714 A1	12/2009	Liu et al.
2008/0069791 A1	3/2008	Beissert	2009/0325916 A1	12/2009	Zhang et al.
2008/0085877 A1	4/2008	Bortz	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0095831 A1	4/2008	McGraw	2010/0028360 A1	2/2010	Atwood
2008/0095838 A1	4/2008	Abou Chakra-Vernet	2010/0034838 A1	2/2010	Staniforth et al.
2008/0113953 A1	5/2008	DeVries et al.	2010/0034880 A1	2/2010	Sintov et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0040671 A1	2/2010	Ahmed et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0048523 A1	2/2010	Bachman et al.
2008/0125402 A1	5/2008	Dilberti	2010/0055138 A1	3/2010	Margulies et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0074959 A1	3/2010	Hansom et al.
2008/0138390 A1	6/2008	Hsu	2010/0086599 A1	4/2010	Chang et al.
			2010/0092568 A1	4/2010	Huempel et al.
			2010/0105071 A1	4/2010	Lerner et al.
			2010/0119585 A1	4/2010	Laufer et al.
			2010/0119585 A1	5/2010	Hille et al.

US 11,103,513 B2

Page 8

(56)

References Cited

U.S. PATENT DOCUMENTS

2010/0129320 A1	5/2010	Phiasivongsa et al.	2011/0312928 A1	12/2011	Nachaegari et al.
2010/0136105 A1	6/2010	Chen et al.	2011/0318405 A1	12/2011	Erwin
2010/0137265 A1	6/2010	Leonard	2011/0318431 A1	12/2011	Gulati
2010/0137271 A1	6/2010	Chen et al.	2012/0009276 A1	1/2012	De Groote
2010/0143420 A1	6/2010	Shenoy et al.	2012/0015350 A1	1/2012	Nabatiyan et al.
2010/0143481 A1	6/2010	Shenoy et al.	2012/0021041 A1	1/2012	Rossi et al.
2010/0150993 A1	6/2010	Theobald et al.	2012/0028888 A1	2/2012	Janz et al.
2010/0152144 A1	6/2010	Hermsmeyer	2012/0028910 A1	2/2012	Combil et al.
2010/0168228 A1	7/2010	Bose et al.	2012/0028936 A1	2/2012	Gloge et al.
2010/0183723 A1	7/2010	Laurent-Applegate et al.	2012/0045532 A1	2/2012	Cohen
2010/0184736 A1	7/2010	Coelingh Bennink et al.	2012/0046264 A1	2/2012	Simes et al.
2010/0190758 A1	7/2010	Fausser et al.	2012/0046518 A1	2/2012	Yoakum et al.
2010/0204326 A1	8/2010	D Souza	2012/0052077 A1	3/2012	Truitt, III et al.
2010/0210994 A1	8/2010	Zarif	2012/0058171 A1	3/2012	De Graaff et al.
2010/0221195 A1	9/2010	Tamarkin et al.	2012/0058962 A1	3/2012	Cumming et al.
2010/0227797 A1	9/2010	Axelson et al.	2012/0058979 A1	3/2012	Keith et al.
2010/0240626 A1	9/2010	Kulkarni et al.	2012/0064135 A1	3/2012	Levin et al.
2010/0247482 A1	9/2010	Cui et al.	2012/0065179 A1	3/2012	Andersson
2010/0247632 A1	9/2010	Dong et al.	2012/0065221 A1	3/2012	Babul
2010/0247635 A1	9/2010	Rosenberg et al.	2012/0087872 A1	4/2012	Tamarkin et al.
2010/0255085 A1	10/2010	Liu et al.	2012/0101073 A1	4/2012	Mannion et al.
2010/0273730 A1	10/2010	Hsu et al.	2012/0121517 A1	5/2012	Song et al.
2010/0278759 A1	11/2010	Murad	2012/0121692 A1	5/2012	Xu et al.
2010/0279988 A1	11/2010	Setiawan et al.	2012/0122829 A1	5/2012	Taravella et al.
2010/0291191 A1	11/2010	Shoichet et al.	2012/0128625 A1	5/2012	Shalwitz et al.
2010/0292199 A1	11/2010	Leverd et al.	2012/0128654 A1	5/2012	Terpstra et al.
2010/0303825 A9	12/2010	Sirbasku	2012/0128683 A1	5/2012	Shantha
2010/0312137 A1	12/2010	Gilmour et al.	2012/0128733 A1	5/2012	Perrin et al.
2010/0316724 A1	12/2010	Whitfield et al.	2012/0128777 A1	5/2012	Keck et al.
2010/0322884 A1	12/2010	Dipietro et al.	2012/0129773 A1	5/2012	Geier et al.
2010/0330168 A1	12/2010	Gicquel et al.	2012/0129819 A1	5/2012	Vancaillie et al.
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0136013 A1	5/2012	Li et al.
2011/0039814 A1	2/2011	Huatan et al.	2012/0142645 A1	6/2012	Marx
2011/0053845 A1	3/2011	Levine et al.	2012/0148670 A1	6/2012	Kim et al.
2011/0066473 A1	3/2011	Bernick et al.	2012/0149748 A1	6/2012	Shanler et al.
2011/0076775 A1	3/2011	Stewart et al.	2012/0172343 A1	7/2012	Lindenthal et al.
2011/0076776 A1	3/2011	Stewart et al.	2012/0184515 A1	7/2012	Klar et al.
2011/0086825 A1	4/2011	Chatroux	2012/0231052 A1	9/2012	Sitruk Ware et al.
2011/0087192 A1	4/2011	Uhland et al.	2012/0232011 A1	9/2012	Kneissel et al.
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0232042 A1	9/2012	Klar et al.
2011/0098258 A1	4/2011	Masini Eteve et al.	2012/0263679 A1	10/2012	Marlow et al.
2011/0098631 A1	4/2011	McIntyre et al.	2012/0269721 A1	10/2012	Weng et al.
2011/0104268 A1	5/2011	Pachot et al.	2012/0269878 A2	10/2012	Cantor et al.
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	2012/0277249 A1	11/2012	Andersson et al.
2011/0130372 A1	6/2011	Agostinacchio et al.	2012/0277727 A1	11/2012	Doshi et al.
2011/0135719 A1	6/2011	Besins et al.	2012/0283671 A1	11/2012	Shibata et al.
2011/0142945 A1	6/2011	Chen et al.	2012/0295911 A1	11/2012	Mannion et al.
2011/0152840 A1	6/2011	Lee et al.	2012/0301517 A1	11/2012	Zhang et al.
2011/0158920 A1	6/2011	Morley et al.	2012/0301538 A1	11/2012	Gordon Beresford et al.
2011/0171140 A1	7/2011	Illum et al.	2012/0302535 A1	11/2012	Caufriez et al.
2011/0182997 A1	7/2011	Lewis et al.	2012/0316130 A1	12/2012	Hendrix
2011/0190201 A1	8/2011	Hyde et al.	2012/0316496 A1	12/2012	Hoffmann et al.
2011/0195031 A1	8/2011	Du	2012/0321579 A1	12/2012	Edelson et al.
2011/0195114 A1	8/2011	Carrara et al.	2012/0322779 A9	12/2012	Voskuhl
2011/0195944 A1	8/2011	Mura et al.	2012/0328549 A1	12/2012	Edelson et al.
2011/0217341 A1	9/2011	Sah	2012/0329738 A1	12/2012	Liu
2011/0238003 A1	9/2011	Bruno Raimondi et al.	2013/0004619 A1	1/2013	Chow et al.
2011/0244043 A1	10/2011	Xu et al.	2013/0011342 A1	1/2013	Tamarkin et al.
2011/0250256 A1	10/2011	Hyun Oh et al.	2013/0017239 A1	1/2013	Viladot Petit et al.
2011/0250259 A1	10/2011	Buckman	2013/0022674 A1	1/2013	Dudley et al.
2011/0250274 A1	10/2011	Shaked et al.	2013/0023505 A1	1/2013	Garfield et al.
2011/0256092 A1	10/2011	Phiasivongsa et al.	2013/0023823 A1	1/2013	Simpson et al.
2011/0262373 A1	10/2011	Umbert Millet	2013/0028850 A1	1/2013	Tamarkin et al.
2011/0262494 A1	10/2011	Achleitner et al.	2013/0029947 A1	1/2013	Nachaegari et al.
2011/0268665 A1	11/2011	Tamarkin et al.	2013/0029957 A1	1/2013	Giliyar et al.
2011/0275584 A1	11/2011	Wilckens et al.	2013/0045266 A1	2/2013	Choi et al.
2011/0281832 A1	11/2011	Li et al.	2013/0045953 A1	2/2013	Sitruk Ware et al.
2011/0287094 A1	11/2011	Penhasi et al.	2013/0059795 A1	3/2013	Lo et al.
2011/0293720 A1	12/2011	General et al.	2013/0064897 A1	3/2013	Binay
2011/0294738 A1	12/2011	Ren et al.	2013/0072466 A1	3/2013	Choi et al.
2011/0300167 A1	12/2011	McMurry et al.	2013/0084257 A1	4/2013	Ishida et al.
2011/0301087 A1	12/2011	McBride et al.	2013/0085123 A1	4/2013	Li et al.
2011/0306579 A1	12/2011	Stein	2013/0089574 A1	4/2013	Schmidt Gollwitzer et al.
2011/0311592 A1	12/2011	Birbara	2013/0090318 A1	4/2013	Ullmann et al.
2011/0312927 A1	12/2011	Nachaegari et al.	2013/0102781 A1	4/2013	Bevill et al.
			2013/0108551 A1	5/2013	Langereis et al.
			2013/0116215 A1	5/2013	Coma et al.
			2013/0116222 A1	5/2013	Arnold et al.
			2013/0122051 A1	5/2013	Abidi et al.

US 11,103,513 B2

Page 9

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2013/0123175 A1	5/2013 Hill et al.	2014/0213565 A1	7/2014 Bernick et al.			
2013/0123220 A1	5/2013 Queiroz	2014/0329783 A1	11/2014 Bernick et al.			
2013/0123351 A1	5/2013 Dewitt	2014/0370084 A1	12/2014 Bernick et al.			
2013/0129818 A1	5/2013 Bernick et al.	2014/0371182 A1	12/2014 Bernick et al.			
2013/0131027 A1	5/2013 Pakkalin et al.	2014/0371183 A1	12/2014 Bernick et al.			
2013/0131028 A1	5/2013 Snyder et al.	2014/0371184 A1	12/2014 Bernick et al.			
2013/0131029 A1	5/2013 Bakker et al.	2014/0371185 A1	12/2014 Bernick et al.			
2013/0149314 A1	6/2013 Bullerdiek et al.	2015/0031654 A1	1/2015 Amadio			
2013/0164225 A1	6/2013 Tamarkin et al.	2015/0045335 A1	2/2015 Bernick et al.			
2013/0164346 A1	6/2013 Lee et al.	2015/0133421 A1	5/2015 Bernick et al.			
2013/0165744 A1	6/2013 Carson et al.	2015/0164789 A1	6/2015 Bernick et al.			
2013/0178452 A1	7/2013 King	2015/0224117 A1	8/2015 Bernick et al.			
2013/0183254 A1	7/2013 Zhou et al.	2015/0224118 A1	8/2015 Bernick et al.			
2013/0183325 A1	7/2013 Bottoni et al.	2015/0302435 A1	10/2015 Bernick et al.			
2013/0189193 A1	7/2013 Tamarkin et al.	2015/0342963 A1	12/2015 Bernick et al.			
2013/0189196 A1	7/2013 Tamarkin et al.	2015/0352126 A1	12/2015 Bernick et al.			
2013/0189230 A1	7/2013 Shoichet et al.	2015/0359737 A1	12/2015 Bernick et al.			
2013/0189368 A1	7/2013 Mosqueira et al.	2016/0030449 A1	2/2016 Persicaner et al.			
2013/0210709 A1	8/2013 McMurry et al.	2016/0213685 A1	7/2016 Bernick et al.			
2013/0216550 A1	8/2013 Penninger et al.	2017/0056418 A1	3/2017 Thorsteinsson et al.			
2013/0216596 A1	8/2013 Viladot Petit et al.	2017/0216310 A1	8/2017 Mirkin et al.			
2013/0224177 A1	8/2013 Kim et al.	2017/0281645 A1	10/2017 Shadiack et al.			
2013/0224257 A1	8/2013 Sah et al.	2017/0281646 A1	10/2017 Inskeep et al.			
2013/0224268 A1	8/2013 Alam et al.	2017/0281647 A1	10/2017 Shadiack et al.			
2013/0224300 A1	8/2013 Maggio	2017/0281776 A1	10/2017 Shadiack et al.			
2013/0225412 A1	8/2013 Sardari Lodriche et al.	2018/0161343 A1	6/2018 Mirkin et al.			
2013/0225542 A1	8/2013 Poegh et al.	2018/0161344 A1	6/2018 Mirkin et al.			
2013/0226113 A1	8/2013 Schumacher et al.	2018/0161345 A1	6/2018 Bernick et al.			
2013/0243696 A1	9/2013 Wang et al.	2018/0221389 A1	8/2018 Amadio et al.			
2013/0245253 A1	9/2013 Marx et al.	2018/0280410 A1	10/2018 Amadio et al.			
2013/0245570 A1	9/2013 Jackson	2018/0289723 A1	10/2018 Bernick et al.			
2013/0261096 A1	10/2013 Merian et al.	2019/0022107 A1	1/2019 Mirkin et al.			
2013/0266645 A1	10/2013 Becker et al.	2019/0046542 A1	2/2019 Bernick et al.			
2013/0267485 A1	10/2013 Da Silva Maia Filho	2019/0070197 A1	3/2019 Amadio et al.			
2013/0273167 A1	10/2013 Lee et al.	2019/0142844 A1	5/2019 Bernick et al.			
2013/0274211 A1	10/2013 Burman et al.	2019/0247401 A1	8/2019 Amadio et al.			
2013/0280213 A1	10/2013 Voskuhl	2019/0314386 A1	10/2019 Bernick et al.			
2013/0316374 A1	11/2013 Penninger et al.	2019/0343771 A1	11/2019 Mirkin et al.			
2013/0317065 A1	11/2013 Tatani et al.	2019/0343845 A1	11/2019 Bernick et al.			
2013/0317315 A1	11/2013 Lu et al.	2019/0358243 A1	11/2019 Mirkin et al.			
2013/0324565 A1	12/2013 Li et al.	2020/0069700 A1	3/2020 Bernick et al.			
2013/0331363 A1	12/2013 Li et al.	2020/0147104 A1	5/2020 Bernick et al.			
2013/0338122 A1	12/2013 Bernick et al.	2020/0217105 A1	6/2020 Bernick et al.			
2013/0338123 A1	12/2013 Bernick et al.	2020/0281940 A1	9/2020 Bernick et al.			
2013/0338124 A1	12/2013 Li et al.	2020/0281941 A1	9/2020 Bernick et al.			
2013/0345187 A1	12/2013 Rodriguez Oquendo	2020/0323881 A1	10/2020 Bernick et al.			
2014/0018335 A1	1/2014 Tatani et al.	FOREIGN PATENT DOCUMENTS				
2014/0024590 A1	1/2014 Weidhaas et al.	CN	102258455 A	11/2011		
2014/0031289 A1	1/2014 Song et al.	EP	0261429 A1	3/1988		
2014/0031323 A1	1/2014 Perez	EP	0275716 A1	7/1988		
2014/0066416 A1	3/2014 Leunis et al.	EP	0279977 A2	8/1988		
2014/0072531 A1	3/2014 Kim et al.	EP	0622075 A1	11/1994		
2014/0079686 A1	3/2014 Birman et al.	EP	0785211 A1	7/1997		
2014/0088051 A1	3/2014 Bernick et al.	EP	0785212 A1	7/1997		
2014/0088058 A1	3/2014 Maurizio	EP	0811381 A1	12/1997		
2014/0088059 A1	3/2014 Perumal et al.	EP	0904064 A1	3/1999		
2014/0094426 A1	4/2014 Drummond et al.	EP	0813412 B1	12/1999		
2014/0094440 A1	4/2014 Bernick et al.	EP	1094781 B1	7/2008		
2014/0094441 A1	4/2014 Bernick et al.	EP	2191833 A1	6/2010		
2014/0099362 A1	4/2014 Bernick et al.	GB	452238 A	8/1936		
2014/0100159 A1	4/2014 Conrad	GB	720561 A	12/1954		
2014/0100204 A1	4/2014 Bernick et al.	GB	848881 A	9/1960		
2014/0100205 A1	4/2014 Bernick et al.	GB	874368 A	8/1961		
2014/0100206 A1	4/2014 Bernick et al.	GB	1589946 A	5/1981		
2014/0113889 A1	4/2014 Connor et al.	IN	2005KOL00053	8/2005		
2014/0127185 A1	5/2014 Stein et al.	IN	216026	3/2008		
2014/0127280 A1	5/2014 Duesterberg et al.	IN	244217	11/2010		
2014/0127308 A1	5/2014 Opara et al.	JP	H2-207024 A	8/1990		
2014/0128798 A1	5/2014 Janson et al.	JP	H4-503810	9/1990		
2014/0148491 A1	5/2014 Valia et al.	JP	H2-264725 A	10/1990		
2014/0186332 A1	7/2014 Ezrin et al.	JP	2002510336 A	4/2002		
2014/0187487 A1	7/2014 Shoichet et al.	JP	2006513182 A	4/2006		
2014/0193523 A1	7/2014 Henry	RU	2155582 C2	9/2000		
2014/0194396 A1	7/2014 Li et al.	RU	2449796 C2	2/2006		
2014/0206616 A1	7/2014 Ko et al.	RU	2317813 C2	2/2008		
		WO	1990011064	10/1990		
		WO	1993017686	9/1993		

US 11,103,513 B2

Page 10

(56)	References Cited				
FOREIGN PATENT DOCUMENTS					
WO	1994022426	10/1994	WO	2006105615	10/2006
WO	WO 1995005807 A1	3/1995	WO	2006113505	10/2006
WO	1995030409	11/1995	WO	2006138686	12/2006
WO	1996009826	4/1996	WO	2006138735	12/2006
WO	1996019975	7/1996	WO	2007045027	4/2007
WO	1996030000	10/1996	WO	2007076144 A2	7/2007
WO	1997005491	2/1997	WO	2007103294	9/2007
WO	1997043989	11/1997	WO	2007120868	10/2007
WO	WO 199740823 A1	11/1997	WO	2007123790	11/2007
WO	1998010293	3/1998	WO	2007124250	11/2007
WO	1998032465	7/1998	WO	2007144151	12/2007
WO	WO 1998041217 A1	9/1998	WO	2008049516	5/2008
WO	1998051280	11/1998	WO	2008152444	12/2008
WO	1999022680 A1	5/1999	WO	2009002542	12/2008
WO	1999032072	7/1999	WO	2009036311	3/2009
WO	1999039700	8/1999	WO	2009040818	4/2009
WO	1999042109	8/1999	WO	2009069006	6/2009
WO	1999043304	9/1999	WO	2009098072	8/2009
WO	1999048477	9/1999	WO	2009133352	11/2009
WO	1999053910	10/1999	WO	2010033188	3/2010
WO	WO 1999052528 A1	10/1999	WO	2010146872	12/2010
WO	WO 1999055333 A1	11/1999	WO	2011000210	1/2011
WO	1999062497 A1	12/1999	WO	2011073995	6/2011
WO	1999063974	12/1999	WO	2011120084	10/2011
WO	2000001351	1/2000	WO	2011128336	10/2011
WO	2000006175	2/2000	WO	2012009778	1/2012
WO	2000038659	6/2000	WO	2012024361	2/2012
WO	2000045795	8/2000	WO	2012055814	5/2012
WO	2000050007	8/2000	WO	2012055840	5/2012
WO	2000059577	10/2000	WO	2012065740	5/2012
WO	2000076522	12/2000	WO	2012098090 A1	7/2012
WO	2001037808	5/2001	WO	2012116277 A1	8/2012
WO	2001054699	8/2001	WO	2012118563 A2	9/2012
WO	2001060325	8/2001	WO	2012120365 A1	9/2012
WO	2001087276	11/2001	WO	2012127501 A2	9/2012
WO	2001091757	12/2001	WO	2012156561 A1	11/2012
WO	2002007700	1/2002	WO	2012156822 A1	11/2012
WO	2002011768	2/2002	WO	2012158483 A2	11/2012
WO	2002022132	3/2002	WO	2012166909 A1	12/2012
WO	2002040008	5/2002	WO	2012170578 A1	12/2012
WO	2002041878	5/2002	WO	2013011501 A1	1/2013
WO	2002053131	7/2002	WO	2013025449 A1	2/2013
WO	2002078602	10/2002	WO	2013028639 A1	2/2013
WO	2002078604	10/2002	WO	2013035101 A1	3/2013
WO	2003028667	4/2003	WO	2013044067 A1	3/2013
WO	2003041718	5/2003	WO	2013045404 A2	4/2013
WO	2003041741	5/2003	WO	2013059285 A1	4/2013
WO	2003068186	8/2003	WO	2013063279 A1	5/2013
WO	2003077923	9/2003	WO	2013102665 A1	7/2013
WO	2003082254	10/2003	WO	2013106437 A1	7/2013
WO	2003092588	11/2003	WO	2013112947 A1	8/2013
WO	2004014397	2/2004	WO	2013113690	8/2013
WO	2004014432	2/2004	WO	2013124415 A1	8/2013
WO	2004017983	3/2004	WO	2013127727 A1	9/2013
WO	2004032897	4/2004	WO	2013127728 A1	9/2013
WO	WO 2004032942 A1	4/2004	WO	2013144356 A1	10/2013
WO	2004052336	6/2004	WO	2013149258 A2	10/2013
WO	2004054540	7/2004	WO	2013158454 A2	10/2013
WO	WO 2004054576 A1	7/2004	WO	2013170052 A1	11/2013
WO	2004080413	9/2004	WO	2013178587 A1	12/2013
WO	2004110408 A2	12/2004	WO	2013181449 A1	12/2013
WO	WO 2004110402 A1	12/2004	WO	2013192248 A1	12/2013
WO	2005027911	3/2005	WO	2013192249	12/2013
WO	2005030175	4/2005	WO	2013192250	12/2013
WO	2005081825	9/2005	WO	2013192251	12/2013
WO	2005087194	9/2005	WO	2014001904 A1	1/2014
WO	2005087199	9/2005	WO	2014004424 A1	1/2014
WO	2005105059	11/2005	WO	2014009434 A1	1/2014
WO	2005115335	12/2005	WO	2014018569 A1	1/2014
WO	2005120470	12/2005	WO	2014018570 A1	1/2014
WO	2005120517	12/2005	WO	2014018571 A2	1/2014
WO	2006013369	2/2006	WO	2014018856 A1	1/2014
WO	2006034090	3/2006	WO	2014018932 A2	1/2014
WO	2006036899	4/2006	WO	2014031958 A1	2/2014
WO	2006053172	5/2006	WO	2014041120 A1	3/2014

US 11,103,513 B2

Page 11

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2014052792	A1	4/2014
WO	2014056897	A1	4/2014
WO	2014066442	A2	5/2014
WO	2014074846	A1	5/2014
WO	2014076231	A1	5/2014
WO	2014076569	A1	5/2014
WO	2014081598	A1	5/2014
WO	2014086739	A1	6/2014
WO	2014093114	A1	6/2014
WO	2014104784	A1	7/2014
WO	2015179782	A1	11/2015
WO	2016018993	A1	2/2016

OTHER PUBLICATIONS

- Co-pending Application, United States U.S. Appl. No. 16/833,186 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/833,188 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/833,213 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/834,780 Inventor, Bernick, B.A., filed Mar. 30, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/834,844 Inventor, Bernick, B.A., filed Mar. 30, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/837,929, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/837,933, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/837,937, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/875,030 Inventor, Bernick, B.A., filed May 15, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/885,066 Inventor, Bernick, B.A., filed May 27, 2020 (Not Published).
- Co-pending Application, U.S. Appl. No. 16/855,094 Inventor, Bernick, B.A., filed May 27, 2020 (Not Published).
- De Vries., T.P.G.M., et al, Guide to Good Prescribing: A Practical Manual, Essential Medicines and Health Products Information Portal, World Health Organization, Annex 3 ("How to explain the use of some dosage forms"), Checklist 11 ("Vaginal tablet without applicator") available at <http://apps.who.int/medicinedocs/en/d/Jwhozip23e/7.3.11.html>, 2 pages, 1994.
- Kingsburg, SA., et al., "Treating dyspareunia caused by vaginal atrophy: a review of treatment options using vaginal estrogen therapy," *International Journal of Women's Health*, 1:105-111, Dove Medical Press Ltd., United Kingdom (2009).
- Martelli, M.E., Vaginal Medicine Administration, The Gale Encyclopedia of Nursing and Allied Health, Gale Group, pp. 2542-2543 (2002).
- Mirkin, S., et al., "The Replenish Trial: Evaluating TX-001HTR ,The First Combination 17 (3-Estradioi/Natural Progesterone Capsule using SYMBODA™ technology), a new option for the treatment of menopausal symptoms," 14th World Congress on Menopause, May 1-4, 2014 in Cancun, Mexico, Therapeutics MD, 1 page.
- Non-Final Office Action dated Feb. 17, 2017, in U.S. Appl. No. 14/719,933, Inventors, Bernick, B.A., filed May 22, 2015, 10 pages.
- Final Office Action dated Oct. 10, 2017, in U.S. Appl. No. 14/719,933, Inventors, Bernick, B.A., filed May 22, 2015, 13 pages.
- Non-Final Office Action dated May 31, 2018, in U.S. Appl. No. 14/719,933, Inventors, Bernick, B.A., filed May 22, 2015, 9 pages.
- Pickar, J.H., et al., "Pharmacokinetics of the First Combination 17B-Estradioi/Progesterone Capsule in Clinical Development for Hormone Therapy," Presented at the 24th annual meeting of the North American Menopause Society, Oct. 9-12, 2013 in Dallas, TX, 1 page.
- PROMETRIUM® (progesterone, USP) prescribing information (Jun. 2009) FDA Label, 33 pages.
- Rioux, J.E., et al, "17 β-Estradiol Vaginal Tablet Versus Conjugated Equine Estrogen Vaginal Cream to Relieve Menopausal Atrophic Vaginitis," *Menopause: The Journal of the North American Menopause Society*, 7(3): 156-161, The North American Menopause Society, United States (2000).
- Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences*, 11(3):42-49, Niper, India (Jul.-Sep. 2010).
- Simon, J.A., et al., "The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone," *Fertility and Sterility*, 60(1):26-33, Elsevier for the American Society for Reproductive Medicine, United States (Jul. 1993).
- VAGIFEM® (estradiol vaginal tablets) prescribing information (Nov. 2009) FDA Label, 14 pages.
- Abbas et al., Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis, *European J of Pharma*, 715 (2013) 72-75, Elsevier.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Acarturk, Fusun, Mucoadhesive Vaginal Drug Delivery System, Recent Patents on Drug Delivery & Formulation, 2009, vol. 3, pp. 193-195.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceutical substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Araya-Sibija et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Araya-Sibija, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), *Scanning* vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibija, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibija, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibija, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, *Menopause: The Journal of the North American Menopause Society*, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, *Advances in Therapy®*, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, *Yale J Bilogy and Medicine*, vol. 35, Feb. 1963, pp. 329-340.
- Azeem, Adnan et al., Microemulsions as a Surrogate Carrier for Dermal Drug Delivery, *Drug Development and Industrial Phar-*

US 11,103,513 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- macy, May 2000, vol. 35, No. 5, pp. 525-547 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/03639040802448646>.
- Azure Pharma, Inc., ELESTRINTM—Estradiol Gel, Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=1-1885>, 26 pages, Aug. 2009.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17 β -estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, Current Medicinal Chemistry, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, Biology of Reproduction 52, 1327-1333 (1995).
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani Bhagu R, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3):756-759.
- Bhavnani et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER α and ER β , Endocrinology, Oct. 2008, 149(10):4857-4870.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductiveaged female subjects, Fertility and Sterility# vol. 94, No. 4, Sep. 2010, Elsevier.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index> [Feb. 3, 2014 1:37:50 PM].
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kinters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moleculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Castelo-Branco Camil et al., "Treatment of atrophic vaginitis," Therapy, 2007, vol. 4, No. 3, pp. 349-353.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- Chambin et al., Interest of Multifunctional Lipid Excipients: Case of Gelucire® 44/14, Drug Development and Industrial Pharmacy, vol. 31, No. 6, pp. 527-534 (Year: 2005).
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Cho, Y.A. et al., Transdermal Delivery of Ketonolac Tromethamine: Effects of Vehicles and Penetration Enhancers, Drug Development and Industrial Pharmacy, 30(6):557-564, Jun. 2004.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, J Clin Oncol 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, Contact Dermatitis 2008: 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, Contact Dermatitis, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance , Contact Dermatitis, 71, 264-272, 2014.
- Chun et al., Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles . . . , J. Kor. Pharm. Sci., vol. 35, No. 3, pp. 173-177 (2005).
- Cicinelli et al., Direct Transport of Progesterone From Vagina to Uterus, Obstetrics & Gynecology, vol. 95, No. 3, March 2000, pp. 403-406.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Committee Opinion, Incidentally Detected Short Cervical Length, Committee of Obstetric Practice, Obstetrics & Gynecology, ACOG, vol. 119, No. 4, Apr. 2012, pp. 879-882.
- Commodari, Fernando, Comparison of 17 β -estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Corn Refiners Association, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Crandall, Carolyn, "Vaginal Estrogen Preparations: A Review of Safety and Efficacy for Vaginal Atrophy," Journal of Women's Health, 2002, vol. 11, No. 10, pp. 857-877.
- CREMER Care, "MIGLYOL® 810, 812 INCI: Caprylic/Capric Triglyceride," CREMER OLEO GmbH & Co. KG, pp. 1-7, available at http://s3.amazonaws.com/petercremerna/products/spec_sheets/159/339/301/_original/MIGL_YOL_81_0_812_TDS.pdf (Mar. 2013) accessed on Dec. 30, 2016.
- Crithley et al., Estrogen Receptor β , But Not Estrogen Receptor α , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, The Journal of Clinical Endocrinology & Metabolism, 2001, vol. 86, No. 3, pp. 1370-1378.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Diramio, Jackie A., Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs, Masters of Science Thesis, University of Georgia, Athens, Georgia, 2002, 131 pages.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, Menopause: The Journal of The North American Menopause Society, 2013, vol. 20, No. 11, pp. 1-7.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.

US 11,103,513 B2

Page 13

- (56) **References Cited**
- OTHER PUBLICATIONS**
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *SciFinder, Pharmaceutica Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Estradiol, The Merck Index Online, Royal Society of Chemistry, <https://www.rsc.org/Merck-Index/monograph/mono1500003758/estradiol?q=unauthorized>.
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GMBH, 2010, 28 pages.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, PiracicabaB1, Braz.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene B 1sed on exposure and effect data, *Contact Dermatitis* 1990; 23: 341-345.
- Fotherby, K., Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, *Contraception*, 1996; 54:59-69.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.*(2013), Elsevier.
- Fuchs et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Cutis*. Jun. 2003;71(6):481-8.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gäfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Ganam-Quintanar et al., Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss, *International Journal of Pharmaceutics*, vo. 147, No. 2, Feb. 28, 1997, pp. 165-171 (abstract only).
- Garad S. et al., "Preclinical Development for Suspensions," A.K. Kulshreshtha et al. (eds.), *Pharmaceutical Suspensions: From Formulation Development to Manufacturing*, Springer, New York 2010, pp. 127-176.
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/B1ck-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Giron-Forest, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Glaser et al., Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al., Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Gunstone, Frank D, et al., *Vegetable Oils in Food Technology: Composition, Properties and Uses*, Blackwell Publishing, CRC Press, 2002.
- Gurney, E.P. et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J.Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane B 1rrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- Haner, Barbara, Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hargrove et al., Menopausal Hormone Replacement Therapy with Continuous Daily Oral Micronize Estradiol and Progesterone, *Obstet Gynecol*, vol. 73, No. 4, Apr. 1989, pp. 606-612.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Sturdy of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.

US 11,103,513 B2

Page 14

(56)

References Cited

OTHER PUBLICATIONS

- Herman, Aima et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, Journal of Pharmacy and Pharmacology, pp. 1-13.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Holm et al., "Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides," European Journal of Pharmaceutical Sciences 20 (2003) 91-97.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hostynk, JJ, Predicting absorption of fragrances through human skin, J. Soc.CosmeCt. hem. 4 6, 221-229 (Jul./Aug. 1 1995).
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Humberstone, Andrew et al., "Lipid-based vehicles for the oral delivery of poorly water soluble drugs," Advanced Drug Delivery Reviews, 25 (1997) 103-128.
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, Journal of Cerebral Blood Flow and Metabolism 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 α -Ethyn Estradiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 β -Estradiol, JPET 290(2):740-747, 1999.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johanson, Gunnar, Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester, Critical Reviews in Toxicology, 2000, vol. 30, No. 3 , pp. 307-345 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/10408440091159220>.
- Johnson, William S, et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, J Reprod Fert (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, Environmental Health Perspectives • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karande, et al. Enhancement of transdermal drug delivery via synergistic action of chemicals, Biochimica et Biophysica Acta, 1788:2362-2373, Sep. 2009.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, Contact Dermatitis, 1992: 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, Ann. Occup. Hyg., vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, Menopause: The Journal of the North American Menopause Society, 2014, vol. 21, No. 6, pp. 1-3.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, B1zedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, Endocrinology 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Kincl et al., Increasing Oral Bioavailability of Progesterone by Formulation, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.
- Knuth et al., Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations, Advanced Drug Delivery Reviews, vol. 11, No. 1-2, Jul.-Aug. 1993, pp. 137-167 (abstract only).
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, European Journal of Pharmaceutics and Biopharmaceutics 64 (2006) 82-91.
- Komm et al., B1zedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, Endocrinology 146(9):3999-4008, 2005.
- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of The Middle East Tech. University, Sep. 2003.
- Kotian, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier (abstract only).
- Kuhnert-Brandstaetter and Grimm. Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II, Mikrochimica Acta, vol. 1, pp. 127-139, 1968.
- Kuhnert-Brandstaetter and Junger and Kofler. Thermo-microscopic and spectrophotometric: Determination of steroid hormones, Microchemical Journal 9, pp. 105-133, 1965.
- Kuhnert-Brandstaetter and Kofler. Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, Mikrochimica Acta, vol. 6, pp. 847-853, 1959.
- Kuhnert-Brandstaetter and Linder. Zur Hydratbildung bei Steroidhormonen, Sci. Pharm, vol. 41(2), pp. 109-116, 1973.
- Kumasaka et al., Effects of Various Forms of Progestin on the the Estrogen-Primed, Ovariectomized Rat, Endocrine Journal 1994, 41(2), 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, Am J Obstet Gynecol. Jul. 2011 ; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, FVV in OBGYN, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, Am J Obstet Gynecol. May 2010 ; 202(5): 455.e1-455.e9.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, Journal of Steroid Biochemistry & Molecular Biology, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , Jour. of Pharm. Sci., vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, Pharmaceutical Research, vol. 22(5) May 2005, Springer Science+Business Media.
- Lane, Majella E., "Skin penetration enhancers," International Journal of Pharmaceutics 447 (2013) 12-21.

US 11,103,513 B2

Page 15

- (56) **References Cited**
- OTHER PUBLICATIONS**
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G. et al., Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women, *Maturitas*, *The European Menopause Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17 α - and 17 β -estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lindmark, Tuulikki et al., "Absorption Enhancement through Intracellular Regulation of Tight Junction Permeability by Medium Chain Fatty Acids in Caco-2 Cells," *JPET* 284(1):362-369, 1998.
- Lindmark, Tuulikki et al., "Mechanisms of Absorption Enhancement by Medium Chain Fatty Acids in Intestinal Epithelial Caco-2 Cell Monolayers," *JPET* 275(2):958-964, 1995.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lopes, Luciana B. et al., Enhancement of transdermal delivery of progesterone using medium-chain mono and diglycerides as skin penetration enhancers, *Pharmaceutical Development and Technology*, 14:5, 524-529, Mar. 2009.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Lucy et al., Gonadotropin-releasing hormone at estrus: lutenizing hormone, estradiol, and progesterone during . . . *Biol Reprod* Sep. 1986;35(2):300-311 (abstract only).
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Mac Bride, Maire B. et al., "Vulvovaginal Atrophy," *Mayo Clin Proc*, Jan. 2010, 85(1):87-94.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Magness, R.R., et al., Estrone, Estradiol-17 β and Progesterone Concentrations in Uterine Lymph and Systematic Blood throughout the Porcine Estrone Estrous Cycle, *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststoping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- McGuffey, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration by Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Monti, D. et al., Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin, *International Journal of Pharmaceutics*, 237:209-24, 2002.
- Mueck, A.O. et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol.Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Ng, Jo-Han et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- NuGen, What is NuGen HP Hair Growth System.
- NuGest900, NuGest 900TM.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical application of pregersterone cream to pre-and post-menopausal women, *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Opinion on the Diethylene Glycol Momoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Panay et al., The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy, *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Panchangnula et al., Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcitol . . . , *J Pharm Pharmacol.* Sep. 1991;43(9):609-614 (abstract only).
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Int'l Union of Crystallography, ISSN 0108-2701, 2003.
- Patel et al., Transdermal Drug Delivery System: A Review, www.thepharmajournal.com, vol. 1, No. 4, 2012, pp. 78-87.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pfau et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.

US 11,103,513 B2

Page 16

(56)

References Cited

OTHER PUBLICATIONS

- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Position Statement, Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society (NAMS), *Menopause*, vol. 20, No. 9, pp. 888-902.
- Potluri, Praveen and Guru V. Betageri, "Mixed-micellar proliposomal systems for enhanced oral delivery of progesterone," *Drug Delivery*, 2006, vol. 13, No. 3, pp. 227-232.
- Practice Bulletin No. 141, Management of Menopausal Symptoms, *Obstetrics & Gynecology*, ACOG, vol. 123, No. 1, Jan. 2014, pp. 202-216.
- Prajapati Hetal N. et al., "A Comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water Phase Diagram, Solubility Determination and Dispersion Testing for Application in Pharmaceutical Dosage Form Development," *Pharm Res.* Jan. 2012; 29(1): 285-305. Published online Aug. 23, 2011. doi: 10.1007/s11095-011-0541-3.
- Prajapati Hetal N. et al., "Effect of Difference in Fatty Acid Chain Lengths of Medium-Chain Lipids on Lipid/Surfactant/Water Phase Diagrams and Drug Solubility," *J. Excipients and Food Chem.* 2 (3) 2011:73-88.
- Prajapati, Hetal N. et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol.* Nov. 2008 ; 26(11): 1261-1268.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Product Information Sheet, Body B1llance Cream, Tahitian Noni International, 2013, 1 page.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Progesterone, The Merck Index Online, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patche s_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause a Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014, 6: 139-143.
- Rao, R. et al., "The Affect of Capmul, Labrafil and Transcutol on Progesterone 100 Mg Soft Capsules Bioavailability in Indian Healthy Adult Postmenopausal Female Subjects Under Fasting Conditions," *Bioequivalence & Bioavailability*, 7(2):095-107, 2015.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181, 512-520 (2014).
- Rosilio, V. et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799,1998, Plenum Pub. Corp.
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *Ann J Obstet Gynecol*, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010;5 943-954, Dove Press.
- Sallee, Verney L. et al., "Determinants of intestinal mucosal uptake of short- and medium-chain fatty acids and alcohols," *Journal of Lipid Research*, 1973, vol. 14, 475-484.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Salole, Eugene G., The physicochemical properties of oestradiol, *Journal of Pharmaceutical & Biomedical Analysis*, vol. 5, No. 7, pp. 635-648, 1987.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, *CLIMACTERIC* 2014;17:1-14.
- Sarkar, Bisu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ B1se . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Sarpal, K. et al., "Self emulsifying drug delivery systems: a strategy to improve oral bioavailability," *Current Research & Information on Pharmaceuticals Sciences (CRIPS)*, 2010, vol. 11, No. 3, pp. 42-49.
- Sarrel, et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, *American Journal of Public Health, Research and Practice*, e1-e6. Published online ahead of print Jul. 18, 2013.
- Satyunarayana, D. et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem.Mol. Biol.* (2013), Elsevier.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, *Maturitas* 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, *Fertil Steril.* Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, *Toxicologic Pathology*, 42: 1188-1196, 2014.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Search Report, Extended European Search Report for EP13741053. 6, dated Jul. 1, 2015.
- Search Report, Extended European Search Report for EP13807188. 1, dated Nov. 23, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US12/66406, dated Jan. 24, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/23309, dated Apr. 9, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46442, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46443, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46444, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46445, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US14/61811, dated Jan. 21, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/23041, dated Jun. 30, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/42621, dated Oct. 29, 2015.

US 11,103,513 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, Journal of Experimental & Clinical Cancer Research 2014, 33(1):41, 11 pages.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
- Shufelt et al., Hormone therapy dose, formulation, route delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014, pp. 1-7, 2013.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, Pharmaceutical Technology, Aug. 2014, pp. 28, 30-31.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmapelridch.com/catalog/product/sigma/p7556>.
- Simon et al., Effective Treatment of Vaginal atrophy with an Ultra-low-dose estradiol vaginal tablet, Obstetrics & Gynecology, vol. 112, No. 5, Nov. 2008, pp. 1053-1060.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? Menopause: The Journal of the North American Menopause Society, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware et al., Progestogens in hormonal replacement therapy: new molecules, risks, and benefits, Menopause: The Journal of the North American Menopause Society. vol. 9, No. 1, pp. 6-15, 2002.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," Maturitas 47 (2004) 277-283.
- Sitruk-Ware, Regine, Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review, Contraception, Oct. 1987, vol. 36, No. 4, pp. 373-402.
- Smith et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, JAMA Internal Medicine, Published online Sep. 30, 2013, E1-E7. jamainternalmedicine.com.
- Smyth et al., Summary of Toxicological Data, A 2-yr Study of Diethylene Glycol Monoethyl Ether in Rats, Fd Cosmet. Toxicol. vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Therapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, Contraception, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," Menopause: The Journal of the North American Menopause Society, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z. et al., Ethynodiol and 17 β -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, Contraception 87 (Jun. 2013) vol. 87, No. 6, pp. 706-727.
- Stanczyk, F.Z., "All progestins are not created equal," Steroids 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" Climacteric 2014;17 (Suppl 2):8-11.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," Int J Pharmaceutical Compounding, vol. 12, No. 4, Jul/Aug. 2008, pp. 295-304.
- Strickley, Robert T., Solubilizing excipients in oral and injectable formulations, Pharmaceutical Research Feb. 2004, vol. 21, Issue 2, pp. 201-230 (abstract only).
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.
- Struhar, M. et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, Alternative Medicine Review vol. 12, No. 3, 2007, pp. 259-264.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helvetiae, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, Biology of Reproduction 31, 399-413 (1984).
- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, Gynecol Endocrinol, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Thomas, Peter, Characteristics of membrane progestin receptor alpha (mPR α) and progesterone membrane receptor component 1 (PGMRC1) and their roles in mediating rapid progestin actions, Frontiers in Neuroendocrinology 29 (2008) 292-312.
- Tripathi, R. et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPPS PhamSciTech, vol. 11, No. 3, Sep. 2010.
- Trommer et al., Overcoming the stratum Corneum: The modulation of Skin Penetration, Skin Pharmacol Physiol 2006;19:106-121.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- Ueda et al., Topical and Transdermal Drug Products, Pharmacopeial Forum, vol. 35(3) [May-Jun. 2009], 750-754.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/uspc29nf24s0_m69870.html, search done: Feb. 25, 2014.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- U.S. Appl. No. 13/843,428, filed Jul. 2, 2015 Non-Final Office Action.

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(56)

References Cited

OTHER PUBLICATIONS

- U.S. Appl. No. 14/106,655, filed Jun. 19, 2015 Final Office Action.
 U.S. Appl. No. 13/684,002, filed Mar. 20, 2013_Non-Final_Office_Action.
 U.S. Appl. No. 13/684,002, filed Jul. 16, 2013_Final_Office_Action.
 U.S. Appl. No. 13/684,002, filed Dec. 6, 2013_Notice_of_Allowance.
 U.S. Appl. No. 13/843,362, filed Mar. 16, 2015_Restriction_Requirement.
 U.S. Appl. No. 13/843,428, filed Apr. 14, 2015_Restriction_Requirement.
 U.S. Appl. No. 14/099,545, filed Feb. 18, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,545, filed Jul. 14, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,562, filed Feb. 20, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,562, filed Mar. 27, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,562, filed Jul. 2, 2014_Final_Office_Action.
 U.S. Appl. No. 14/099,562, filed Dec. 10, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,571, filed Mar. 28, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,571, filed Jul. 15, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,582, filed Apr. 29, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,582, filed Jun. 17, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,582, filed Nov. 7, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,582, filed Jan. 22, 2015_Notice_of_Allowance.
 U.S. Appl. No. 14/099,598, filed May 13, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,598, filed Jul. 3, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,598, filed Dec. 10, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,612, filed Mar. 20, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,612, filed Oct. 30, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,612, filed Nov. 26, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,623, filed Mar. 5, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,623, filed Jul. 18, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,623, filed Dec. 15, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/106,655, filed Jul. 3, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/106,655, filed Dec. 8, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/125,554, filed Dec. 5, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/125,554, filed Apr. 14, 2015_Non-Final_Office_Action.
 U.S. Appl. No. 14/136,048, filed Nov. 4, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/136,048, filed Mar. 12, 2015_Non-Final_Office_Action.
 U.S. Appl. No. 14/475,814, filed Oct. 1, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/475,814, filed Feb. 13, 2015_Notice_of_Allowance.
 U.S. Appl. No. 14/475,864, filed Oct. 2, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/475,864, filed Feb. 11, 2015_Notice_of_Allowance.
 U.S. Appl. No. 14/476,040, filed Mar. 26, 2015_Restriction_Requirement.
 U.S. Appl. No. 14/521,230, filed Dec. 5, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/521,230, filed Feb. 18, 2015_Non-Final_Office_Action.
 U.S. Appl. No. 14/624,051, filed Apr. 7, 2015_Non-Final_Office_Action.
 Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens, Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
 Voegtlle et al., Dispatches from the interface of salivary bioscience and neonatal research, Frontiers in Endocrinology, Mar. 2014, vol. 5, article 25, 8 pages.
 Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, Journal of Steroid Biochemistry & Molecular Biology 80 (2002) 449-455.
 Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role For the Lung, Biology of Reproduction 40, 1188-1193 (1989).
 Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, Reproduction (2005) 129 765-777.
 Weber, E.J., Corn Lipids, Cereal Chem., vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
 Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
 Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," Forbes, Feb. 20, 2015; retrieved online at <http://onforbes/1LIUm1V>, on Feb. 23, 2015, 3 pages.
 Whitehead et al., Absorption and metabolism of oral progesterone, The British Medical Journal, vol. 280, No. 6217 (Mar. 22, 1980), pp. 825-827, BMJ Publishing Group.
 Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
 Wood et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, Breast Cancer Res Treat (2007) 101:125-134.
 Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, Climacteric, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
 Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, Biology of Reproduction 69, 1308-1317 (2003).
 Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
 Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, 2003, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
 Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
 Zava, David T. et al., Percutaneous absorption of progesterone, Maturitas 77 (2014) 91-92, Elsevier.
 Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. http://www.zrlab.com/component/docman/cat_view/10-publications?Itemid.

* cited by examiner

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Semi-logarithmic Plot of Mean Plasma Free Estradiol (Corrected) Concentrations Versus Time (N=62)

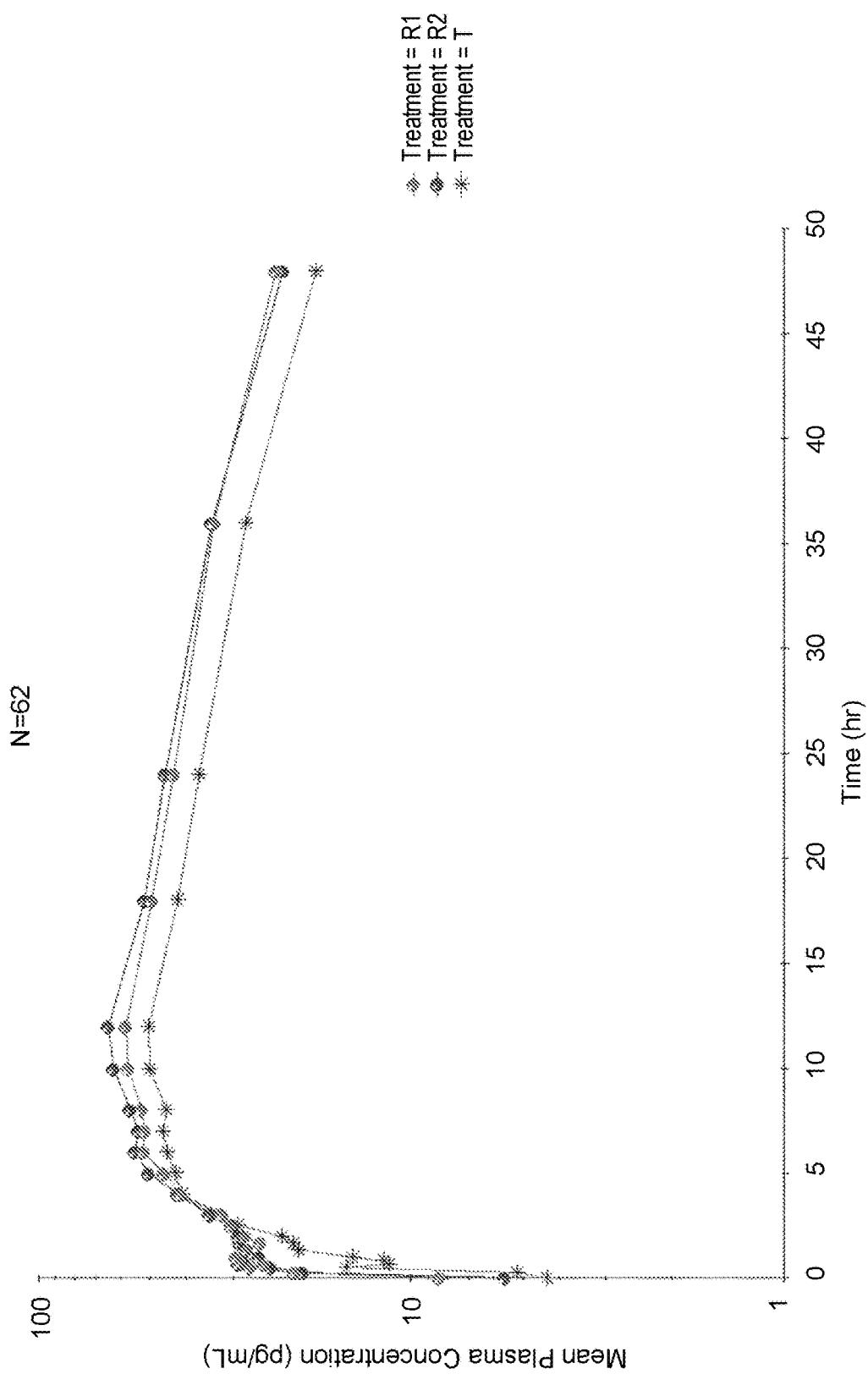


FIG. 1

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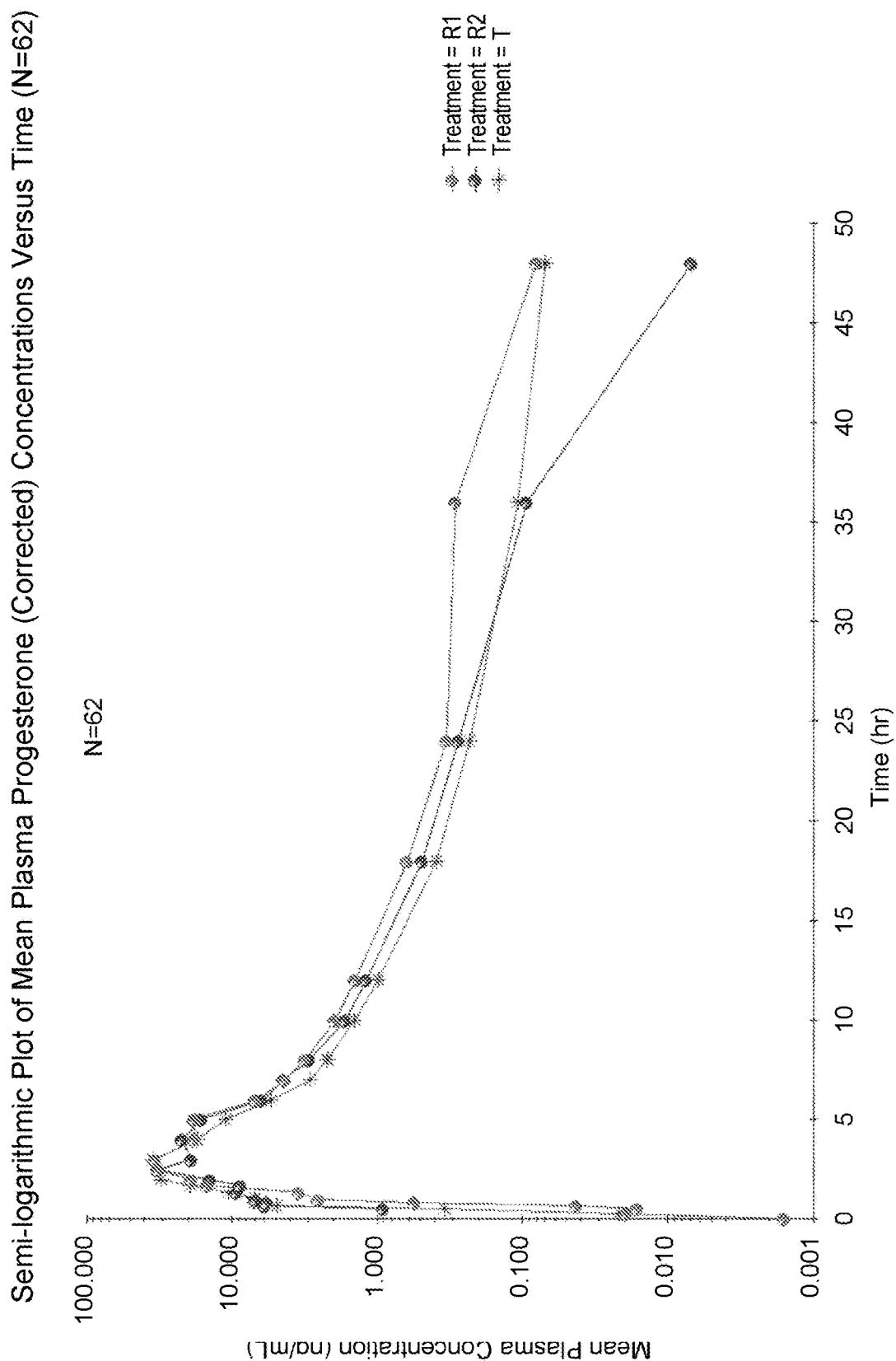


FIG. 2

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Semi-logarithmic Plot of Mean Plasma Free Estrone Concentrations Versus Time (N=62)

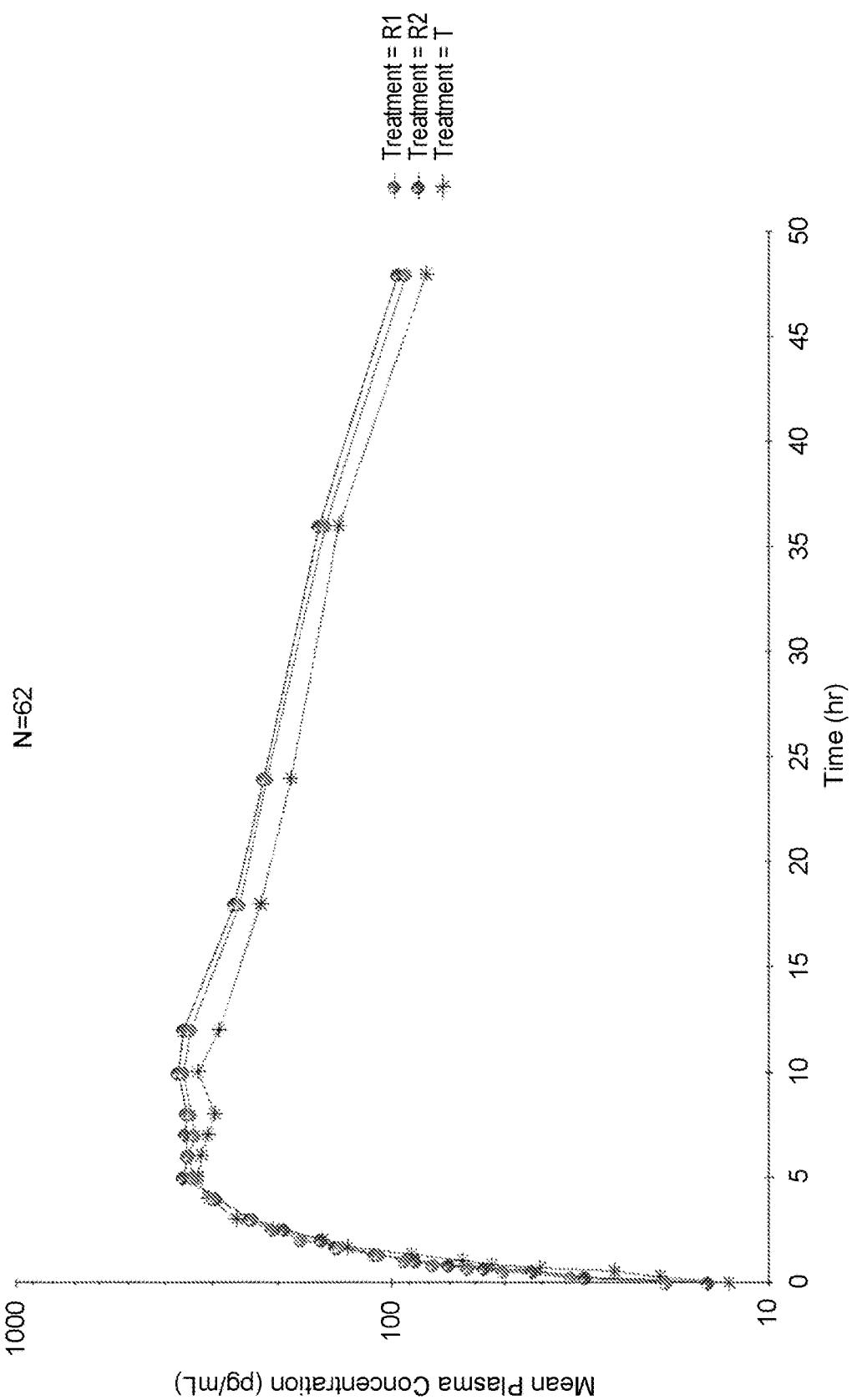


FIG. 3

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Semi-logarithmic Plot of Mean Plasma Total Estrone (Corrected) Concentrations Versus Time (N=61)

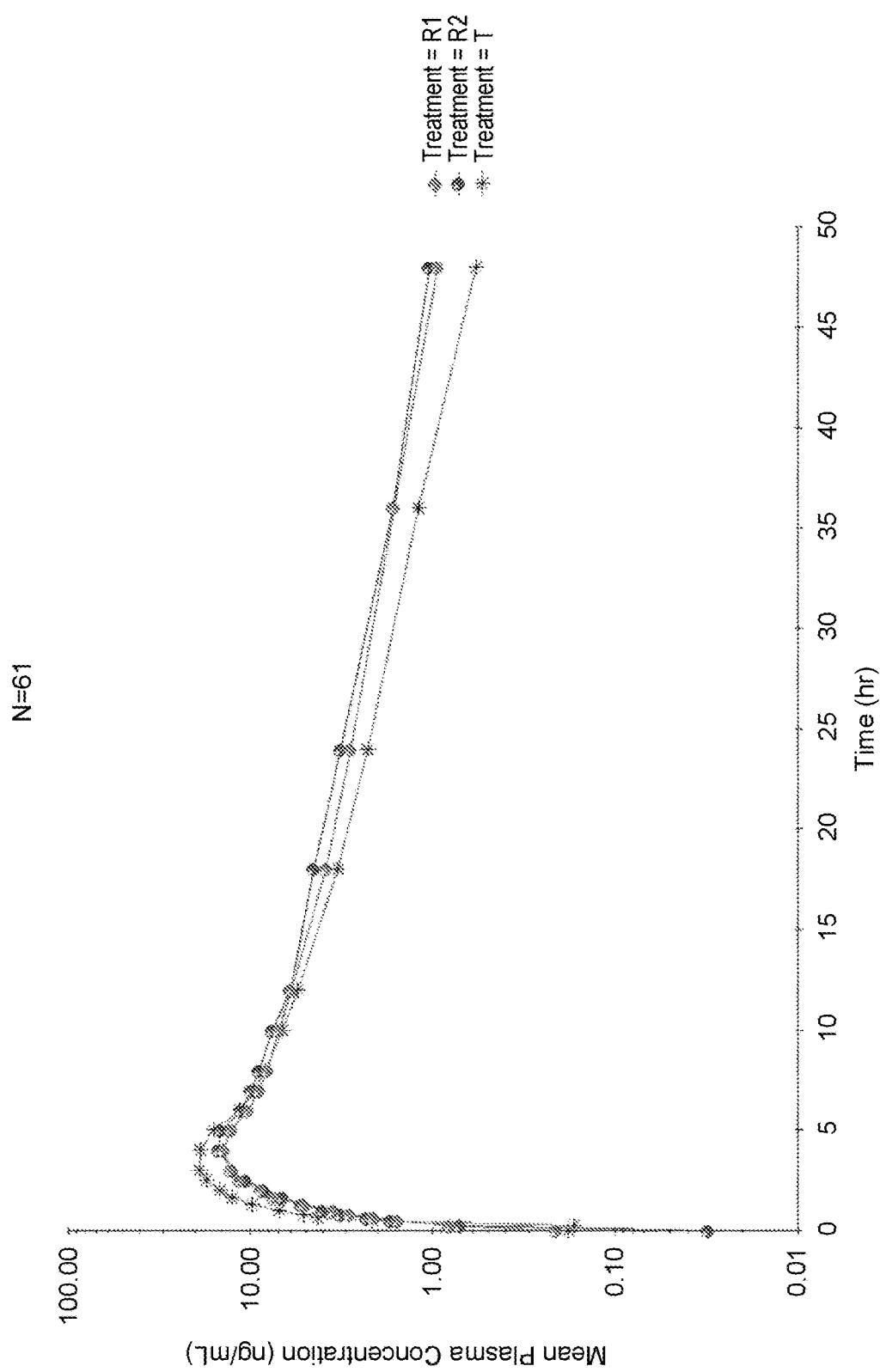


FIG. 4

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a divisional of U.S. patent application Ser. No. 14/719,933, filed May 22, 2015, which claims priority to U.S. Provisional Application Ser. No. 62/002,090, filed May 22, 2014, the content of each of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

This application relates to pharmaceutical compositions and methods for hormone replacement therapy.

BACKGROUND OF THE INVENTION

Hormone Replacement Therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones in a pre-menopausal, peri-menopausal, menopausal or post-menopausal subject.

BRIEF SUMMARY OF THE INVENTION

In one aspect, pharmaceutical compositions for co-administering estradiol and progesterone to a subject in need of natural hormone replacement therapies are provided. In some embodiments, the pharmaceutical composition comprises: solubilized estradiol, suspended progesterone, and a solubilizing agent, wherein the solubilizing agent is a medium chain (C6-C12) oil and wherein the pharmaceutical composition, when administered to a subject, produces in a plasma sample from the subject one or more pharmacokinetic parameters as described herein (e.g., an area under the curve (AUC)_(0-t) or a C_{max} for estradiol, progesterone, estrone, or total estrone as described herein, e.g., in Tables 18-21).

In some embodiments, the pharmaceutical composition comprises a solubilizing agent that comprises a glyceride of at least one C6-C12 fatty acid. In some embodiments, the glyceride ester is a mixture of mono- and diglycerides (e.g., glyceryl caprylate/caprate). In some embodiments, the fatty acid is predominantly a C8 to C10 fatty acid. In some embodiments, the pharmaceutical composition further comprises a surfactant (e.g., lauroyl polyoxyglyceride). In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.25 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition com-

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prises estradiol at a dosage of about 1 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 2 mg and comprises progesterone at a dosage of about 200 mg.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve (AUC)_(0-t) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an AUC_(0-t) for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an AUC_(0-t) for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; and a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an AUC_(0-t) for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an AUC_(0-t) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- (ii) one or both of (a) an AUC_(0-t) for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an AUC_(0-t) for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- (iv) one or both of (a) an AUC_(0-t) for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an AUC_(0-t) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an AUC_(0-t) for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the

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subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and

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(ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally

- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 1 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml, and a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, and a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition has the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, the pharmaceutical composition has the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, the pharmaceutical composition has the blood plasma estrone concentration profile of

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FIG. 3. In some embodiments, the pharmaceutical composition has the blood plasma total estrone concentration profile of FIG. 4.

In some embodiments, the one or more parameters as described herein (e.g., the $AUC_{(0-t)}$ or C_{max} for progesterone, estradiol, estrone, or total estrone) are measured at regular intervals (e.g., about every 30 minutes, about every 60 minutes, or about every 90 minutes) or at irregular intervals over a period of time such as 24 hours or 48 hours. In some embodiments, the one or more parameters as described herein (e.g., the $AUC_{(0-t)}$ or C_{max} for progesterone, estradiol, estrone, or total estrone) are measured at about 0.25 hr, 0.5 hr, 0.67 hr, 0.83 hr, 1 hr, 1.33 hr, 1.67 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, or 48 hr after administering the pharmaceutical composition to the subject. In some embodiments, the one or more parameters as described herein are measured at regular or irregular intervals following the administration of a single dose or of a first dose of the pharmaceutical composition to the subject.

In another aspect, methods of treating a subject are provided. In some embodiments, the subject has a condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause, such as vasomotor symptoms). In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil as described herein, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein. In some embodiments, the method comprises administering a pharmaceutical composition comprising estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprising progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the method comprises administering a pharmaceutical composition comprising: estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 100 mg; estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg; or estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549

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pg/ml to 66.6483 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- 10 (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- 15 (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- 20 (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- 25 (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- 30 (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- 35 (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- 40 (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally

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- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ($AUC_{(0-t)}$) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to

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266.5933 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a C_{max} for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In still another aspect, pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil, wherein the treatment produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein (e.g., an $AUC_{(0-t)}$ or C_{max} for estradiol, progesterone, estrone, or total estrone as described herein, e.g., as described in any of Tables 18-21). In some embodiments, the pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency comprise estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprise progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 18 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 19 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a

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dosage of about 0.50 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 20 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 21 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estradiol.

FIG. 2 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for progesterone.

FIG. 3 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estrone.

FIG. 4 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for total estrone.

DETAILED DESCRIPTION OF THE INVENTION

In the following detailed description of embodiments of this disclosure, reference is made to the accompanying drawings in which like references indicate similar elements, and in which is shown, by way of illustration, specific embodiments in which this disclosure may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice this disclosure, and it is to be understood that other embodiments may be utilized and that other changes may be made without departing from the scope of this disclosure. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of this disclosure is defined only by the appended claims. As used in this disclosure, the term “or” shall be understood to be defined as a logical disjunction (i.e., and/or) and shall not indicate an exclusive disjunction unless expressly indicated as such with the term “either,” “unless,” “alternatively,” and words of similar effect.

I. DEFINITIONS

The term “area under the curve” (“AUC”) refers to the area under the curve defined by changes in the blood, plasma, or serum concentration of an active pharmaceutical ingredient (e.g., estradiol or progesterone), or one or more metabolites of the active pharmaceutical ingredient, over time following the administration of a dose of the active pharmaceutical ingredient. “ $AUC_{0-\infty}$ ” is the area under the concentration-time curve extrapolated to infinity following the administration of a dose. “ AUC_{0-t} ” is the area under the concentration-time curve from time zero to time t following the administration of a dose, wherein t is the last time point with measurable concentration.

The term “ C_{max} ” refers to the maximum value of blood, plasma, or serum concentration shown on the curve that represents changes in blood, plasma, or serum concentrations of an active pharmaceutical ingredient (e.g., progesterone or estradiol), or one or more metabolites of the active pharmaceutical ingredient, over time.

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The term “ T_{max} ” refers to the time that it takes for the blood, plasma, or serum concentration of an active pharmaceutical ingredient (e.g., estradiol or progesterone), or of one or more metabolites of the active pharmaceutical ingredient, to reach the maximum value.

Collectively, AUC, C_{max} , and, optionally, T_{max} are the principal pharmacokinetic parameters that can characterize the pharmacokinetic response of a particular drug product, such as progesterone or estradiol, in an animal, especially a mammal, including human, subject.

An “active pharmaceutical ingredient” (API), as used herein, means the active compound or compounds used in formulating a drug product. APIs are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “bioavailability” has the meaning as defined in 21 C.F.R. § 320.1(a): the rate and extent to which an API or active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the API or active ingredient or active moiety becomes available at the site of action. For example, bioavailability can be measured as the amount of API in the blood (whole blood, serum, or plasma) as a function of time. In embodiments, the amount of API is measured in blood plasma. Pharmacokinetic (PK) parameters such as AUC, C_{max} , or T_{max} may be used to measure and assess bioavailability.

The term “bioequivalent” has the meaning as defined in 21 C.F.R. § 320.1(e): the absence of a significant difference in the rate and extent to which the API or active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms or modified release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. In practice, two products are considered bioequivalent if the 90% confidence interval of the AUC, C_{max} , or optionally T_{max} is within 80.00% to 125.00%.

The term “bio-identical hormone” or “body-identical hormone” refers to an active pharmaceutical ingredient that is structurally identical to a hormone naturally or endogenously found in the human body (e.g., estradiol and progesterone).

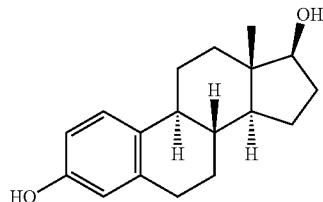
The term “estrogen” refers to a group of several female sex hormones produced primarily by the ovaries, including estradiol, estrone, and estriol. As used herein, unless otherwise specified, estrogen refers to estradiol.

The term “estradiol” refers to (17 β)-estr-1,3,5(10)-triene-3,17-diol. Estradiol is also interchangeably called 17 β -estradiol, oestradiol, or E2, and is found endogenously in the human body. As used herein, estradiol refers to the

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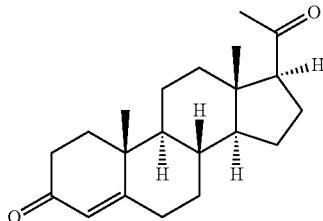
bio-identical or body-identical form of estradiol found in the human body having the structure:



As used herein, unless specified, estradiol includes estradiol in anhydrous or hemihydrate forms. For the purposes of this disclosure, the anhydrous form or the hemihydrate form can be substituted for the other by accounting for the water or lack of water according to well-known and understood techniques.

The term "solubilized estradiol" means that the estradiol or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. Solubilized estradiol may include estradiol that is about 80% solubilized, about 85% solubilized, about 90% solubilized, about 95% solubilized, about 96% solubilized, about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. In some embodiments, the estradiol is "fully solubilized" with all or substantially all of the estradiol being solubilized or dissolved in the solubilizing agent. Fully solubilized estradiol may include estradiol that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The term "progesterone" refers to pregn-4-ene-3,20-dione. Progesterone is also interchangeably called P4 and is found endogenously in the human body. As used herein, progesterone refers to the bio-identical or body-identical form of progesterone found in the human body having the structure:



The term "solubilized progesterone" means that the progesterone or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein disclosed herein. In some embodiments, the progesterone is "partially solubilized" with a portion of the progesterone being solubilized or dissolved in the solubilizing agent and a portion of the progesterone being suspended in the solubilizing agent. Partially solubilized progesterone may include progesterone that is about 1% solubilized, about 5% solubilized, about 10% solubilized, about 15% solubilized, about 20% solubilized, about 30% solubilized, about 40% solubilized, about 50% solubilized, about 60% solubilized, about 70% solubilized, about 80% solubilized, about 85% solubilized, about 90% solubilized or about 95% solubilized. In other embodiments, the progesterone is "fully

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"solubilized" with all or substantially all of the progesterone being solubilized or dissolved in the solubilizing agent. Fully solubilized progesterone may include progesterone that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The terms "micronized progesterone" and "micronized estradiol," as used herein, include micronized progesterone and micronized estradiol, respectively, having an X50 particle size value below about 15 microns or having an X90 particle size value below about 25 microns.

The term "X50" means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "solubilizing agent" refers to an agent or combination of agents that solubilize an active pharmaceutical ingredient (e.g., estradiol or progesterone). For example and without limitation, suitable solubilizing agents include medium chain oils and other solvents and co-solvents that solubilize or dissolve an active pharmaceutical ingredient to a desirable extent. Solubilizing agents suitable for use in the formulations disclosed herein are pharmaceutical grade solubilizing agents (e.g., pharmaceutical grade medium chain oils). It will be understood by those of skill in the art that other excipients or components can be added to or mixed with the solubilizing agent to enhance the properties or performance of the solubilizing agent or resulting formulation. Examples of such excipients include, but are not limited to, surfactants, emulsifiers, thickeners, colorants, flavoring agents, etc. In some embodiments, the solubilizing agent is a medium chain oil and, in some other embodiments, the medium chain oil is combined with a co-solvent(s) or other excipient(s).

The term "medium chain" is used to describe the aliphatic chain length of fatty acid containing molecules. "Medium chain" specifically refers to fatty acids, fatty acid esters, or fatty acid derivatives that contain fatty acid aliphatic tails or carbon chains that contain between 6 (C6) and 14 (C14) carbon atoms.

The terms "medium chain fatty acid" and "medium chain fatty acid derivative" are used to describe fatty acids or fatty acid derivatives with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. Fatty acids consist of an unbranched aliphatic tail attached to a carboxylic acid functional group. Fatty acid derivatives include, for example, fatty acid esters and fatty acid containing molecules, including, without limitation, mono-, di- and triglycerides that include components derived from fatty acids as well as fatty acid esters of ethylene or propylene glycol. Those of skill will appreciate that the aliphatic tails can be saturated or unsaturated (one or more double bonds between carbon atoms). In some embodiments, the aliphatic tails are saturated (i.e., no double bonds between carbon atoms). Medium chain fatty acids or medium chain fatty acid derivatives include those with aliphatic tails having 6-14 carbons, including those that are C6-C14, C6-C12, C8-C14, C6-C10, C8-C10, or others. In embodiments, medium chain fatty acids or medium chain fatty acid derivatives are those that are saturated. Examples include, without limitation, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, and derivatives thereof.

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The term “oil,” as used herein, refers to any pharmaceutically acceptable oil, and specifically excluding peanut oil, that can suspend or solubilize any suitable progesterone or estradiol, starting material, or precursor, including micronized progesterone or estradiol as described herein.

The term “medium chain oil” refers to an oil wherein the composition of the fatty acid fraction of the oil is substantially medium chain (i.e., C6 to C14) fatty acids, i.e., the composition profile of fatty acids in the oil is substantially medium chain. As used herein, “substantially” means that between 20% and 100% (inclusive of the upper and lower limits) of the fatty acid fraction of the oil is made up of medium chain fatty acids, i.e., fatty acids with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. In some embodiments, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 85%, about 90% or about 95% of the fatty acid fraction of the oil is made up of medium chain fatty acids. Those of skill in the art that will readily appreciate that the terms “alkyl content” or “alkyl distribution” of an oil can be used in place of the term “fatty acid fraction” of an oil in characterizing a given oil or solubilizing agent, and these terms are used interchangeable herein. As such, medium chain oils suitable for use in the formulations disclosed herein include medium chain oils wherein the fatty acid fraction of the oil is substantially medium chain fatty acids, or medium chain oils wherein the alkyl content or alkyl distribution of the oil is substantially medium chain alkyls (C6-C12 alkyls). It will be understood by those of skill in the art that the medium chain oils suitable for use in the formulations disclosed herein are pharmaceutical grade (e.g., pharmaceutical grade medium chain oils). Examples of medium chain oils include, for example and without limitation, medium chain fatty acids, medium chain fatty acid esters of glycerol (e.g., for example, mono-, di-, and triglycerides), medium chain fatty acid esters of propylene glycol, medium chain fatty acid derivatives of polyethylene glycol, and combinations thereof.

The term “ECN” or “equivalent carbon number” means the sum of the number of carbon atoms in the fatty acid chains of an oil, and can be used to characterize an oil as, for example, a medium chain oil or a long-chain oil. For example, tripalmitin (tripalmitic glycerol), which is a simple triglyceride containing three fatty acid chains of 16 carbon atoms, has an ECN of $3 \times 16 = 48$. Conversely, a triglyceride with an ECN=40 may have “mixed” fatty acid chain lengths of 8, 16, and 16; 10, 14, and 16; 8, 14, and 18; etc. Naturally occurring oils are frequently “mixed” with respect to specific fatty acids, but tend not to contain both long chain fatty acids and medium chain fatty acids in the same glycerol backbone. Thus, triglycerides with ECNs of 21-42 typically contain predominantly medium chain fatty acids; while triglycerides with ECNs of greater than 43 typically contain predominantly long chain fatty acids. For example, the ECN of corn oil triglyceride in the US Pharmacopeia (USP) would be in the range of 51-54. Medium chain diglycerides with ECNs of 12-28 will often contain predominantly medium chain fatty acids, while diglycerides with ECNs of 32 or greater will typically contain predominantly long chain fatty acids. Monoglycerides will have an ECN that matches the chain length of the sole fatty acid chain. Thus, monoglyceride ECNs in the range of 6-14 contain mainly medium chain fatty acids, and monoglycerides with ECNs of 15 or greater will contain mainly long chain fatty acids.

The average ECN of a medium chain triglyceride oil is typically 21-42. For example, as listed in the USP, medium

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chain triglycerides have the following composition as the exemplary oil set forth in the table below:

5	Fatty Acid Tail Length	% of Oil	Exemplary Oil
	6	<2.0	2.0
	8	50.0-80.0	70.0
	10	20.0-50.0	25.0
	12	<3.0	2.0
10	14	<1.0	1.0

and would have an average ECN of $3 * [(6 * 0.02) + (8 * 0.070) + (10 * 0.25) + (12 * 0.02) + (14 * 0.01)] = 25.8$. The ECN of the exemplary medium chain triglycerides oil can also be expressed as a range (per the ranges set forth in the USP) of 24.9-27.0. For oils that have mixed mono-, di-, and triglycerides, or single and double fatty acid glycols, the ECN of the entire oil can be determined by calculating the ECN of each individual component (e.g., C8 monoglycerides, C8 diglycerides, C10 monoglycerides, and C10 diglycerides) and taking the sum of the relative percentage of the component multiplied by the ECN normalized to a monoglyceride for each component. For example, the oil having C8 and C10 mono- and diglycerides shown in the table below has an ECN of 8.3, and is thus a medium chain oil:

30	Fatty Acid Chain Length	% of Oil	ECN as % of Oil [(chain length) × (% in oil)]	ECN as % of Oil Normalized to Monoglyceride
	C8 monoglyceride	47	$8 \times 0.47 = 3.76$	3.76
	C10 monoglyceride	8	$10 \times 0.08 = 0.8$	0.8
	C8 diglyceride	38	$2 \times (8 \times 0.38) =$ 6.08	$6.08 / 2 = 3.04$
35	C10 diglyceride	7	$2 \times (10 \times 0.07) =$ 1.4	$1.4 / 2 = 0.7$
OIL ECN (normalized to monoglycerides)				8.3

40 Expressed differently, ECN can be calculated as each chain length in the composition multiplied by its relative percentage in the oil: $(8 * 0.85) + (10 * 0.15) = 8.3$.

The term “excipients,” as used herein, refers to non-active pharmaceutical ingredients such as solubilizing agents, anti-oxidants, oils, lubricants, and others used in formulating pharmaceutical products.

45 The terms “treat,” “treating,” and “treatment” refer to any indicia of success in the treatment or amelioration of an injury, disease, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, disease, or condition more tolerable to the patient; slowing in the rate of degeneration or decline; or improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms 50 can be based on objective or subject parameters, including the results of a physical examination, neuropsychiatric examinations, or psychiatric evaluation.

II. PHARMACEUTICAL COMPOSITIONS

60 In one aspect, this disclosure relates to pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof. In some embodiments, the composition comprises estradiol, progesterone, and a solubilizing agent (e.g., a medium chain oil, e.g., a C6-C12 oil). In some embodiments, a pharmaceutical composition comprising estradiol, progesterone, and a solubi-

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lizing agent as described herein, when administered to a subject or a population of subjects, produces one or more AUC, C_{max}, or T_{max} parameters for estradiol, progesterone, estrone, or total estrone as described below.

Formulations of Estradiol and Progesterone Compositions

In some embodiments, a pharmaceutical composition for use as described herein comprises solubilized estradiol with suspended progesterone; solubilized estradiol with both partially solubilized progesterone and partially suspended progesterone; or solubilized estradiol with fully solubilized progesterone. In some embodiments, the composition comprises solubilized estradiol and suspended progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone, although the natural or bio-identical forms of estradiol and progesterone are preferred.

In some embodiments, the composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg. In some embodiments, the composition comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately 80% to 100% soluble in a solubilizing agent, including specifically embodiments that are: 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% soluble in a solubilizing agent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %). In some embodiments, estradiol is micronized. In some embodiments, micronized estradiol has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In some embodiments, micronized estradiol has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. In some embodiments, the composition comprises micronized and partially solubilized estradiol.

In some embodiments, the composition comprises micronized progesterone. The progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size.

Estradiol and progesterone compositions and methods of preparing such compositions are described in U.S. Pat. No. 8,633,178; U.S. Publication No. 2013/0129818; U.S. Publication No. 2013/0338123; International Publication No. WO 2013/078422; and International Publication No. WO 2013/192251; each of which is incorporated by reference in its entirety.

Solubilizing Agents

Estradiol and progesterone compositions of the present disclosure are prepared via blending with a solubilizing agent. In some embodiments, the solubilizing agent is a pharmaceutically acceptable oil that comprises a medium

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chain oil. In some embodiments, the solubilizing agent is a medium chain oil comprised substantially of C6-C12 medium chains, e.g., at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the chains present in the oil are C6-C12. In some embodiments, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids having at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. In some embodiments, the medium chain oil comprises at least one medium chain fatty acid or propylene glycol, polyethylene glycol, or glyceride having esters of medium chain fatty acids. In some embodiments, the solubilizing agent is not peanut oil.

In some embodiments, oils used to solubilize estradiol and to suspend, partially suspend and partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In some embodiments, the medium chain fatty acids are C6, C8, C10, C12, C6-C12, C8-C12, C6-C10, C8-C10, or C10-C12 fatty acids. In some embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 50% saturated, greater than about 60% saturated, or greater than about 75% saturated. In some embodiments, a solubilizing agent comprises predominantly medium chain length, saturated fatty acids or derivatives thereof, specifically predominantly C8 to C12 saturated fatty acids or derivatives thereof.

In some embodiments, medium chain solubilizing agents include, for example and without limitation, saturated medium chain fatty acids or derivatives of saturated medium chain fatty acids: caproic acid (C6), enanthic acid (C7), caprylic acid (C8), pelargonic acid (C9), capric acid (C10), undecylic acid (C11), lauric acid (C12), tridecyllic acid (C13), or myristic acid (C14). In some embodiments, the solubilizing agent comprises oils made of these free medium chain fatty acids, oils of medium chain fatty acid esters of glycerin, propylene glycol, or ethylene glycol, or combinations thereof. These examples comprise predominantly saturated medium chain fatty acids (i.e., greater than 50% of the fatty acids are medium chain saturated fatty acids). In some embodiments, the solubilizing agent comprises predominantly C6 to C12 saturated fatty acids or derivatives of fatty acids.

In some embodiments, the solubilizing agent comprises one or more mono-, di-, or triglycerides or combinations thereof. Exemplary glycerin based solubilizing agents include MIGLYOLS®, which are caprylic/capric triglycerides (SASOL Germany GMBH, Hamburg). MIGLYOLS® includes MIGLYOL® 810 (caprylic/capric triglyceride), MIGLYOL® 812 (caprylic/capric triglyceride), MIGLYOL® 816 (caprylic/capric triglyceride), and MIGLYOL® 829 (caprylic/capric/succinic triglyceride). Other caprylic/capric triglyceride solubilizing agents are likewise contemplated, including, for example: caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; or caprylic/capric/succinic triglycerides. Other exemplary caprylic/capric mono-, di-, or triglyceride solubilizing agents include CAPMULS® (ABITEC, Columbus, Ohio), including, but are not limited to, CAPMUL® MCM, CAPMUL® MCM C10, CAPMUL® MCM C8, CAPMUL® MCM C8 EP, and CAPMUL® 708 G. Other mono-, di-, and triglycerides of fractionated vegetable fatty acids, and combinations or derivatives thereof can be the solubilizing agent, according to embodiments. For example, the solubilizing agent can be 1,2,3-propanetriol (glycerol,

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glycerin, glycerine) esters of saturated coconut and palm kernel oil and derivatives thereof.

In some embodiments, the solubilizing agent comprises one or more esters of propylene glycol, polyethylene glycol, or combinations thereof. Exemplary propylene and polyethylene glycol based solubilizing agents include glyceryl mono- and di-caprylates; propylene glycol monocaprylate (e.g., CAPMUL® PG-8 or CAPMUL® PG-8 NF); propylene glycol monocaprate (e.g., CAPMUL® PG-10); propylene glycol monolaurate (e.g., CAPMUL® PG-12 EP/NF); propylene glycol mono- and dicaprylates; propylene glycol mono- and dicaprate; propylene glycol dicaprylate/dicaprate (e.g., MIGLYOL® 840); propylene glycol dilaurate (e.g., CAPMUL® PG-2L EP/NF); diethylene glycol mono ester (e.g., TRANSCUTOL®, 2-(2-Ethoxyethoxy)ethanol, GATTEFOSSÉ SAS, Saint-Priest, France); and diethylene glycol monoethyl ether.

In some embodiments, commercially available fatty acid glycerol and glycol ester solubilizing agents are prepared from natural oils and therefore may comprise components in addition to the fatty acid esters that predominantly comprise and characterize the solubilizing agent. Such other components may be, e.g., other fatty acid mono-, di-, and triglycerides, fatty acid mono- and diester ethylene or propylene glycols, free glycerols or glycols, or free fatty acids. For example, the Technical Data Sheet by ABITEC for CAPMUL® MCM C8 describes CAPMUL® MCM C8 as being composed of mono- and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as ≤1% C6, ≥95% C8, ≤5% C10, and ≤1.5% C12 and higher. By way of further example, MIGLYOL® 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

In some embodiments, the pharmaceutical composition comprises about 20% to about 85% solubilizing agent by weight, e.g., about 60% to about 85% solubilizing agent by weight. In some embodiments, the composition comprises progesterone, e.g., dissolved and micronized, from about 20 to about 50 wt %, e.g., about 30 to about 35 wt %. In some embodiments, the composition comprises estradiol from about 0.1 to about 0.8 wt %, e.g., about 0.15 to about 0.40 wt %.

Surfactants

In some embodiments, the pharmaceutical composition further comprises one or more non-ionic or ionic surfactants. In some embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of medium chain fatty acids or long chain fatty acids, for example, lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE®, including, for example, GELUCIRE® 39/01 (glycerol esters of saturated C12-C18 fatty acids); GELUCIRE® 43/01 (hard fat NF/JPE); GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, lauroyl polyoxylglycerides (USA FDA IIG)); and GELUCIRE® 50/13 (stearoyl macrogol-32 glycerides EP, stearoyl polyoxyl-32 glycerides NF, stearoyl polyoxylglycerides (USA FDA IIG)).

In some embodiments, non-ionic surfactants comprise combinations of mono- and di-propylene and ethylene glycols and mono-, di-, and triglyceride combinations. For example, in some embodiments, polyethylene glycol glyceride (GELUCIRE®, GATTEFOSSE SAS, Saint-Priest, France) can be used herein as the surfactant. For example,

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GELUCIRE® 44/14 (PEG-32 glyceryl laurate EP), a medium chain fatty acid esters of polyethylene glycol, is a polyethylene glyceride composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

In some embodiments, non-ionic surfactants include, for example and without limitation: one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In some embodiments, non-ionic surfactants comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids.

In some embodiments, non-ionic surfactants include PEG-6 palmitostearate and ethylene glycol palmitostearate, which are available commercially as TEFOSE® 63 (GATTEFOSSÉ SAS, Saint-Priest, France), which can be used with, for example, CAPMUL® MCM having ratios of MCM to TEFOSE® 63 of, for example, 8:2 or 9:1. Other exemplary solubilizing agents/non-ionic surfactants combinations include, without limitation: MIGLYOL® 812:GELUCIRE 50/13 or MIGLYOL® 812:TEFOSE® 63.

A non-ionic or ionic surfactant may be used at concentrations greater than about 0.01%, for example at a concentration of about 0.01%-10.0%, about 0.1% to 10.0%, or about 1% to 10.0%. In some embodiments, the pharmaceutical composition comprises about 10.0% surfactant by weight. In some embodiments, the pharmaceutical composition comprises about 0.1% to about 5.0% surfactant by weight, e.g., about 1.0 wt %.

Other Excipients

In some embodiments, the pharmaceutical composition further comprises one or more other excipients, such as but not limited to colorants, flavoring agents, preservatives, and taste-masking agents. The choice of excipients will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipients on solubility and stability, and the nature of the dosage form. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Generally, the solubilizing agents, surfactants, and excipients used in the pharmaceutical compositions described herein are non-toxic, pharmaceutically acceptable, compatible with each other, and maintain stability of the pharmaceutical composition and the various components with respect to each other. Additionally, the combination of various components that comprise the pharmaceutical compositions will maintain will result in the desired therapeutic effect when administered to a subject.

Formulation

In some embodiments, combinations of solubilizing agents (e.g., two or more oils) or combinations of one or more solubilizing agents and one or more surfactants are used to form estradiol and progesterone compositions. Various ratios of these solubilizing agents or solubilizing agents and surfactants can be used. For example, CAPMUL® MCM and a non-ionic surfactant, e.g., GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP; lauroyl polyoxyl-32 glycerides NF; lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to about 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. As another example, CAPMUL® MCM and a non-ionic surfactant, e.g., TEFOSE® 63, can be used as ratios of about 8:2 or 9:1. Other exemplary solubilizing agent/surfactant combi-

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nations include, without limitation: MIGLYOL® 812:GE-LUCIRE® 50/13 or MIGLYOL® 812:TEFOSE® 63. The ratios of oil (e.g., medium chain fatty acid esters of mono-glycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, CAPMUL® MCM and GELUCIRE® can be used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1.

In some embodiments, estradiol or progesterone is soluble in the solubilizing agent at room temperature, although it may be desirable to warm certain solubilizing agents. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL® MCM) and polyethylene glycol glycerides (e.g., GELUCIRE®) as a surfactant, the oil or the surfactant can be warmed up, e.g., to about 65° C. for the surfactant and less for the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature, or at lower temperatures as the mixture cools, e.g., about 40° C. or about 30° C., or even after the mixture has cooled to room temperature. The progesterone can also be added as the mixture cools, e.g., to below about 40° C. or to below about 30° C., or after the mixture has cooled to room temperature.

As a non-limiting example, a composition of this disclosure comprises solubilized estradiol; progesterone, at least 30% (e.g., at least about 30%, about 40%, about 50%, about 60%, about 70%, about 75%, about 80%, about 85%, or more) of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein); and a solubilizing agent that is an oil, wherein the oil comprises medium chain fatty acid mono-, di-, or triglycerides, with or without a surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with CAPMUL® MCM NF (glyceryl caprylate/caprate) as a solubilizing agent and GELUCIRE® 44/14 (lauroyl poly-oxyglyceride) as a surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following five formulations A-E:

TABLE 1

Pharmaceutical Composition A - progesterone 50 mg/estradiol 0.25 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
CAPMUL ® MCM, NF	65.49	98.24
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

TABLE 2

Pharmaceutical Composition B - progesterone 50 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52

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TABLE 2-continued

Pharmaceutical Composition B - progesterone 50 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
CAPMUL ® MCM, NF	65.32	97.98
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

TABLE 3

Pharmaceutical Composition C - progesterone 100 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
CAPMUL ® MCM, NF	65.49	196.48
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

TABLE 4

Pharmaceutical Composition D - progesterone 100 mg/estradiol 1 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
CAPMUL ® MCM, NF	65.32	195.97
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

TABLE 5

Pharmaceutical Composition E - progesterone 200 mg/estradiol 2 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
CAPMUL ® MCM, NF	65.32	391.94
GELUCIRE ® 44/14, NF	1.00	6.00
Total	100.00	600.00

* Note:
1.00 mg Estradiol is equivalent to 1.03 mg Estradiol Hemihydrate

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono-, di-, or triglycerides, such as CAPMUL® MCM, and 0.5 to 10 wt % of a non-ionic surfactant, such as GELUCIRE® 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, MIGLYOL® 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g.,

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at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more, is solubilized appear to provide improved PK-related properties.

Pharmacokinetic Parameters of Estradiol and Progesterone Compositions

The pharmaceutical compositions of this disclosure can be formulated to provide desirable pharmacokinetic parameters in a subject (e.g., a female subject) to whom the composition is administered. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for progesterone in the subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for estradiol in the subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for one or more metabolites of progesterone or estradiol in the subject, for example, estrone or total estrone.

Following the administration of a composition comprising progesterone and estradiol to a subject, the concentration and metabolism of progesterone or estradiol can be measured in a sample (e.g., a blood, serum, or plasma sample) from the subject. Progesterone is metabolized to pregnane-diols and pregnanolones, which are then conjugated to glucuronide and sulfate metabolites that are excreted or further recycled. Estradiol is converted reversibly to estrone, and both estradiol and estrone can be converted to the metabolite estriol. In postmenopausal women, a significant proportion of circulating estrogens exist as sulfate conjugates, especially estrone sulfate. Thus, estrone can be measured with respect to "estrone" amounts (excluding conjugates such as estrone sulfate) and "total estrone" amounts (including both free, or unconjugated, estrone and conjugated estrone such as estrone sulfate).

The pharmaceutical compositions of this disclosure can be characterized for one or more pharmacokinetic parameters of progesterone, estradiol, or a metabolite thereof following administration of the composition to a subject or to a population of subjects. These pharmacokinetic parameters include AUC, C_{max} , and T_{max} . AUC is a determination of the area under the curve (AUC) plotting the blood, serum, or plasma concentration of drug along the ordinate (Y-axis) against time along the abscissa (X-axis). AUCs are well understood, frequently used tools in the pharmaceutical arts and have been extensively described. C_{max} is well understood in the art as an abbreviation for the maximum drug concentration in blood, serum, or plasma of a subject. T_{max} is well understood in the art as an abbreviation for the time to maximum drug concentration in blood, serum, or plasma of a subject.

In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for estradiol. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for progesterone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for estrone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC, C_{max} , or T_{max} , is measured for total estrone.

Any of a variety of methods can be used for measuring the levels of progesterone, estradiol, estrone, or total estrone in a sample, including immunoassays, mass spectrometry (MS), high performance liquid chromatography (HPLC) with ultraviolet fluorescent detection, liquid chromatography in conjunction with mass spectrometry (LC-MS), tandem mass spectrometry (MS/MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). In some

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embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured using a validated LC-MS/MS method. Methods of measuring hormone levels are well described in the literature.

5 The levels of progesterone, estradiol, estrone, or total estrone can be measured in any biological sample, e.g. a tissue or fluid such as blood, serum, plasma, or urine. In some embodiments, the sample is blood or plasma. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 0.0, 0.10, 0.20, 0.05, 10 0.30, 0.35, 0.40, 0.45, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, or 48 hours after dosing, or any other appropriate time period that is common or useful in determining the levels of each of the hormones. 15 In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of a single dose or a first dose. Generally, assays to 20 determine the levels of progesterone, estradiol, estrone, or total estrone are measured one or more times every 5, 10, 15, 20, 30, 60, 120, 360, 480, 720, or 1440 minutes after administration, or combinations thereof (e.g., the first measurements are taken every 15 minutes for the first hour, followed by every 120 minutes thereafter). In embodiments, the timing of such measurements are designed to accurately measure C_{max} , T_{max} , or AUC. Timing can be adjusted based on the given circumstances (i.e., one formulation may cause 25 a more rapid C_{max} in which case the initial times would be clustered closer together, closer to time zero, or both to ensure accurate measurement of C_{max} , T_{max} , and AUC). In some embodiments, the C_{max} , T_{max} , or AUC values for progesterone, estradiol, estrone, or total estrone are measured 30 following administration of a single dose of a pharmaceutical composition as described herein.

In some embodiments, the values for C_{max} , T_{max} , or AUC represent a number of values taken from all the subjects in 40 a patient population and are, therefore, mean values (e.g., arithmetic or geometric means) averaged over the entire population.

In some embodiments, oral administration of a pharmaceutical composition comprising estradiol, progesterone, and a medium chain solubilizing agent as described herein 45 to a subject, or to a population of subjects, produces one or more AUC, C_{max} , or T_{max} parameters, or one or more mean AUC, mean C_{max} , or mean T_{max} parameters, respectively, for estradiol, progesterone, estrone, or total estrone as described below.

50 AUC, C_{max} , and T_{max} Parameters (A)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises 55 the formulation of Formulation A in Table 1 above.

In some embodiments, administration of a composition comprising about 0.25 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- 60 (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

In some embodiments, administration of the composition 65 to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, and a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

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In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml;

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(ii) a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; or

(iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml;

10 (ii) a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; or

(iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, a mean C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml, a mean C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml, a mean C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

45 In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

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In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a C_{max} for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a C_{max} for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; or a C_{max} for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC, C_{max} , and T_{max} Parameters (B)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation B in Table 2 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or

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(iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii).

In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some

embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml;
- (ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 280.7467

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pg·hr/ml to 438.6667 pg·hr/ml, a mean C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, a mean C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a C_{max} for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for

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total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC , C_{max} , and T_{max} Parameters (C)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation C in Table 3 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i)

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and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml;
- (ii) a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood and plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, a mean C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

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In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation C in Table 3 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation C in Table 3 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a C_{max} for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a C_{max} for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a C_{max} for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC , C_{max} , and T_{max} Parameters (D)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation D in Table 4 above.

In some embodiments, administration of a composition comprising about 1 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; or
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

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In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, and a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

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(i) an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;

(ii) a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; or

(iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml;

(ii) a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; or

(iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, a mean C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml, a mean C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, a mean C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953

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ng·hr/ml; a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/m; a C_{max} for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a C_{max} for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a C_{max} for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and a C_{max} for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

AUC , C_{max} , and T_{max} Parameters (E)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation E in Table 5 above.

In some embodiments, administration of a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml; or
- (ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml, and a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; or
- (ii) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml, and a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml;
- (ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; or

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(iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a T_{max} for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml;
- (ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;
- (iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; or
- (iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii).

In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml;
- (ii) a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; or
- (iii) a T_{max} for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml
- (ii) a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml; or
- (iii) a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml, a mean C_{max} for estradiol that is from 52

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pg/ml to 81 pg/ml, and a mean T_{max} for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml, a mean C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml, and a mean T_{max} for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml, a mean C_{max} for estrone that is from 341 pg/ml to 533 pg/ml, and a mean T_{max} for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml, a mean C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml, and a mean T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml; a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml; a T_{max} for estradiol that is from 7.2 hr to 11.3 hr; an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; a T_{max} for progesterone that is from 2.4 hr to 3.8 hr; an $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml; a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; a T_{max} for estrone that is from 4.4 hr to 6.9 hr; an $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml; a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml; and a T_{max} for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), and measuring one or more pharmacokinetic parameters selected from an $AUC_{(0-t)}$ for estradiol, a C_{max} for estradiol, an $AUC_{(0-t)}$ for progesterone, a C_{max} for progesterone, an $AUC_{(0-t)}$ for estrone, a C_{max} for estrone, an $AUC_{(0-t)}$ for total estrone, and a C_{max} for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml; a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; an $AUC_{(0-t)}$ for estrone that is from 7277 pg·hr/ml to 11370 pg·hr/ml; a C_{max} for estrone that is from 341 pg/ml to 533 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 161 ng·h/ml to 252 ng·h/ml; and a C_{max} for total estrone that is from 28 ng/ml to 44 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

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In some embodiments, administration of the pharmaceutical composition as described herein results in the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, administration of the pharmaceutical composition results in the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, administration of the pharmaceutical composition results in the blood plasma estrone concentration profile of FIG. 3. In some embodiments, administration of the pharmaceutical composition results in the blood plasma total estrone concentration profile of FIG. 4.

Administration and Treatment

Pharmaceutical compositions comprising estradiol and progesterone as described herein (e.g., compositions comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent) can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Pharmaceutical compositions can be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, intrathecal, rectal, vaginal, sublingual or parenteral administration, including subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, or intraurethral injection or infusion. In some embodiments, administration is by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally.

For preparing pharmaceutical compositions from the compounds of this disclosure, the pharmaceutically acceptable compositions can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid preparation can comprise one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. ("Remington's").

In general, the type of composition is selected based on the mode of administration. A pharmaceutical composition (e.g., for oral administration or delivery by injection) can be in the form of a liquid (e.g., an elixir, syrup, solution, emulsion or suspension). Alternatively, a pharmaceutical composition as described herein can take the form of a pill, tablet, or capsule containing the liquid oil, and thus, the composition can contain any of the following: a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof. The composition can also be formulated into a suppository disposed, for example, in a polyethylene glycol (PEG) solubilizing agent.

Administration of the compositions of this disclosure can be carried out via any of the accepted modes of administration. Thus, administration can be, for example, intravenous, topical, subcutaneous, transcutaneous, transdermal, intramuscular, oral, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, or by inhalation. In some embodiments, a composition as described herein is

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administered orally. For example, a pharmaceutical composition as described herein can be administered via capsules such as soft capsules.

In some embodiments, a pharmaceutical composition as described herein is administered once daily for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 days or more. In some embodiments, a pharmaceutical composition as described herein is administered daily for at least one week, at least two weeks, at least three weeks, at least four weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least twelve months, or more. In some embodiments, a pharmaceutical composition as described herein is administered as a continuous-combined therapy regimen.

In some embodiments, a 28-day or monthly regimen of daily doses is packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. In some embodiments, each daily dose contains both estradiol and progesterone. In some embodiments, one or more of the daily doses contains no estradiol or no progesterone. Daily doses that comprise no estradiol or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating the blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized or partially solubilized, or fully solubilized progesterone or solubilized estradiol in amounts as set forth herein, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of daily doses.

In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating conditions in subjects caused, at least in part, by estrogen deficiency, particularly for women with a uterus. For example, in embodiments, the pharmaceutical compositions disclosed herein are useful for the treatment of one or more of the following conditions: endometrial hyperplasia; secondary amenorrhea; prevention of preterm birth, when the subject has a shortened cervix; menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental progesterone or estrogen. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating vasomotor symptoms, including but not limited to, hot flashes and night sweats. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes and night sweats.

In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes. Thus, in some embodiments, this disclosure provides methods of treating such a condition by administering to the subject a composition comprising estradiol and progesterone as described herein.

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III. EXAMPLES

The following examples are offered to illustrate, but not to limit, the claimed subject matter.

Example 1

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition comprising suspended progesterone and solubilized estradiol:

TABLE 6

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL® MCM, NF		82.57	577.97
GELUCIRE® 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

The encapsulated pharmaceutical composition of Table 6 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas (N_2). Mixing or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL® MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.±2° C. GELUCIRE® 44/14 may be added to the CAPMUL® MCM and mixed until dissolved (to increase the solubility of progesterone in the final solution, GELUCIRE® 44/14 was added at about 10% w/w). The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the GELUCIRE® 44/14 and the CAPMUL® MCM.

Heat may be removed from the GELUCIRE® 44/14 and CAPMUL® MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the GELUCIRE® 44/14, CAPMUL® MCM and Estradiol Hemihydrate mixture until dissolved.

The addition may occur all at once or may occur gradually over a period of time.

Example 2

An example of the final scale-up formulation is provided in Table 7. To manufacture, CAPMUL® MCM is heated to 40° C. GELUCIRE® 44/14 is heated to 65° C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until fully suspended.

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TABLE 7

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL® MCM, NF		82.57	577.97	5.78
4.	GELUCIRE® 44/14, NF		10.0	70.00	0.70
Total:		100.00	700.00	7.00	

Example 3

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 8

Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL® MCM, NF		73.371	146.74	1467.42
4.	GELUCIRE® 44/14, NF		1.500	3.00	30.00
Total:		100.000	200.00	mg 2000.0	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 4

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 9

Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL® MCM, NF		65.32	391.93	3919.3
4.	GELUCIRE® 44/14, NF		1.00	6.0	60.0
Total:		100.00	600.0	mg 6000.0	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill.

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The resulting pharmaceutical composition is encapsulated in soft gelatin capsules. Alternatively, GELUCIRE® 44/14 is heated to 65° C. and CAPMUL® MCM is heated to 40° C.±5° C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40° C.; the mixture is then passed through a colloid mill one or more times, e.g., three times.

Example 5

Pharmacokinetics of the First Combination 17β-Estradiol/Progesterone Capsule in Clinical Development for Hormone Therapy

The objective of this study was to evaluate the pharmacokinetic and oral bioavailability of a combination capsule of 17β-estradiol/progesterone in comparison to co-administration of the individual products ESTRACE® and PROMETRIUM®.

Subjects and Study Design: An open label, balanced, randomized, single-dose, 2-treatment, 3-period, 3-sequence, crossover, partial replicate, reference-scaled, oral, relative bioavailability study compared the bioavailability of an investigational 2-mg 17β-estradiol/200-mg progesterone combination capsule, without peanut oil (formulated in a manner similar to that set forth in Table 9), with that of co-administered 200-mg PROMETRIUM® (progesterone) and 2-mg ESTRACE® (17β-estradiol) tablets in healthy postmenopausal women aged 40-65 years (N=66). Key inclusion criteria for subjects included a BMI 18.50 to 29.99 kg/m² who were nonsmokers or ex-smokers (no smoking in the last 3 months). Key exclusion criteria for subjects included consuming grapefruit juice or poppy-containing foods within 48 hours before and throughout the study, use of any hormonal agent within 14 days before the study, and use of menopausal hormone therapy within 6 months before dosing.

Patients were randomly assigned sequentially to 1 of 3 dosing sequences of the same dose of the combination capsule (Test, T) and reference products (Reference, R): TRR, RTR, or RRT. 66 subjects were randomized and 62 (94.0%) completed the study. Subjects had a mean age of 49.5±5.6 years (range 40 to 64) and a mean BMI of 24.8±3.1 kg/m² (range 18.7-29.9).

After consuming a high-fat, high-calorie breakfast, each woman received a single dose of the combination (Test) capsule in 1 period of the study and single doses of the co-administered products (Reference) in each of the 2 remaining periods. Blood samples were collected within 75 minutes before dosing and post-dose at 0.25, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 hours after dosing to determine progesterone, free (unconjugated) estradiol, and free and total (conjugated+free, including estrone sulfates) estrone concentrations. After collection of blood samples at each time point, the blood samples were centrifuged at 4000 RPM for 10 minutes at 4° C. to separate the plasma. The plasma from samples was separated into two aliquots. 1.5 mL from the plasma sample was transferred into aliquot I, and the remaining plasma sample was transferred into aliquot II. These aliquots were stored at -30° C. for interim storage, then at -70° C. until completion of the analysis.

Progesterone, estradiol, estrone, and total estrone in human plasma was determined using the LC-MS/MS method. The primary (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) and secondary (T_{max} , $t_{1/2}$, and K_e) PK parameters for each analyte were determined for each subject during each period

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by non-compartment analyses using baseline-adjusted concentrations. Statistical analyses were conducted using the SAS® statistical software.

Results: The mean, standard deviation (SD), geometric mean, coefficient of variation (CV %), minimum, median, and maximum were calculated for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, K_{el} , K_{el_lower} , K_{el_Upper} , and $AUC\%_{Extrap_obs}$ for progesterone, estradiol, estrone, and total estrone. The

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results are presented in Tables 10, 11, 12, and 13 below. For each of Tables 10-13, “Test Product (T)” refers to the progesterone+estradiol pharmaceutical composition, while “Reference product (R1)” and “Reference product (R2)” refers to co-administered PROMETRIUM® (progesterone) and ESTRACE® (estradiol). Blood plasma concentrations of progesterone, estradiol, estrone, and total estrone over time are also shown in FIGS. 1-4.

TABLE 10

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Progesterone						
PK Parameter	Untransformed Data (Mean ± SD)					
	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
C_{max} (ng/mL)	62	89.2222 ± 149.7309	62	72.7228 ± 101.8885	62	69.7590 ± 87.0777
AUC_{0-t} (ng · hr/mL)	62	120.0869 ± 164.1385	62	125.9406 ± 152.3483	62	111.5867 ± 113.3200
$AUC_{0-\infty}$ (ng · hr/mL)	57	131.3817 ± 172.4806	57	142.1332 ± 160.4853	56	126.6006 ± 117.2665
T_{max} (hr)	62	3.00(0.83-10.00)	62	3.00(1.00-12.00)	62	4.00(0.67-18.00)
K_{el} (hr ⁻¹)	57	0.3064 ± 0.2427	57	0.2684 ± 0.1912	56	0.2795 ± 0.2475
$t_{1/2}$ (hr)	57	4.6445 ± 4.5366	57	5.1555 ± 4.9794	56	5.0389 ± 4.5887
K_{el_Lower} (hr ⁻¹)	57	7.6667 ± 4.6047	57	7.4123 ± 4.2164	56	7.9018 ± 3.9120
K_{el_Upper} (hr ⁻¹)	57	16.2218 ± 11.0051	57	19.1728 ± 12.3801	56	18.1975 ± 10.0858
AUC_{Extra} (%)	57	4.3374 ± 2.5528	57	4.8416 ± 3.7526	56	5.1868 ± 4.1434

*Expressed in terms of median (range)

TABLE 11

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Estradiol			
PK Parameter	Untransformed Data (Mean ± SD)		
	Test Product (T)	Reference product (R1)	Reference product (R2)
C_{max} (pg/mL)	64.7902 ± 50.9833	69.1286 ± 33.0484	73.4236 ± 43.4077
AUC_{0-t} (pg · hr/mL)	1403.7333 ± 763.8136	1508.2206 ± 876.7390	1658.2502 ± 976.5556
$AUC_{0-\infty}$ (pg · hr/mL)	2459.4394 ± 4498.2737	2842.8805 ± 4582.6502	2110.9591 ± 1175.3995
T_{max} (hr)	9.00(0.50-36.00)	10.0(0.50-35.12)	10.00(0.25-36.60)
K_{el} (hr ⁻¹)	0.04380±0.0197	0.0457 ± 0.0358	0.0464 ± 0.0338
$t_{1/2}$ (hr)	31.9104 ± 95.9769	25.0908 ± 28.8346	20.8774 ± 12.0825
K_{el_Lower} (hr ⁻¹)	14.9472 ± 7.2715	14.9667 ± 7.0150	14.7953 ± 5.8774
K_{el_Upper} (hr ⁻¹)	45.3602 ± 6.3668	44.3277 ± 7.4003	43.8330 ± 7.6449
AUC_{Extra} (%)	22.8106 ± 16.6498	25.4773 ± 20.2911	24.9566 ± 16.4713

*Expressed in terms of median (range)

TABLE 12

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R ₁ , R ₂) for Free Estrone			
PK Parameter	Untransformed Data (Mean ± SD)		
	Test Product (T)	Reference product (R1)	Reference product (R2)
C_{max} (pg/mL)	426.5492 ± 179.3303	455.5107 ± 189.448	467.2302 ± 207.4373
AUC_{0-t} (pg · hr/mL)	9096.0907 ± 4377.2730	10156.0282 ± 5140.5831	10507.3557 ± 5183.1289
$AUC_{0-\infty}$ (pg · hr/mL)	11994.9695 ± 6678.5468	13445.9048 ± 8699.4068	14066.2362 ± 7563.2370
T_{max} (hr)	5.50(0.83-36.00)	8.00(1.67-18.00)	10.00(1.67-18.00)
K_{el} (hr ⁻¹)	0.0399 ± 0.0146	0.0424 ± 0.0172	0.0406 ± 0.0209
$t_{1/2}$ (hr)	20.3172 ± 9.4052	19.4595 ± 9.8711	20.7515 ± 9.3985
K_{el_Lower} (hr ⁻¹)	13.8443 ± 7.0649	14.8871 ± 6.6459	14.9194 ± 6.4485
K_{el_Upper} (hr ⁻¹)	46.0238 ± 5.5080	46.2547 ± 5.3060	46.2244 ± 5.3126
AUC_{Extra} (%)	21.2980 ± 11.2283	20.3648 ± 11.1060	21.8900 ± 11.8537

*Expressed in terms of median (range)

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TABLE 13

 Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R₁, R₂) for Total Estrone

PK Parameter	N	Test Product (T)		N	Reference product (R1)		N	Reference product (R2)	
C _{max} (ng/mL)	61	35.4289 ± 17.0856	61	19.8716 ± 7.4485	61	19.9048 ± 8.0288			
AUC _{0-t} (ng · hr/mL)	61	201.7524 ± 94.2081	61	182.7729 ± 88.8386	61	199.8295 ± 94.9392			
AUC _{0-∞} (ng · hr/mL)	61	213.2402 ± 104.6011	60	193.6387 ± 100.5831	56	203.0289 ± 81.4884			
T _{max} (hr)	61	2.50(0.67-7.00)	61	4.00(1.33-18.00)	61	4.00(1.33-10.00)			
K _{el} (hr ⁻¹)	61	0.0799 ± 0.0398	60	0.0803 ± 0.0399	56	0.0718 ± 0.0243			
t _{1/2} (hr)	61	10.3619 ± 4.0023	60	9.8448 ± 3.0702	56	10.7830 ± 3.6624			
K _{el_Lower} (hr ⁻¹)	61	13.0492 ± 6.8585	60	13.5945 ± 8.0129	56	11.8870 ± 6.8696			
K _{el_Upper} (hr ⁻¹)	61	45.3979 ± 6.6589	60	46.3775 ± 5.2525	56	46.7054 ± 4.3888			
AUC_Extra (%)	61	4.5030 ± 3.7366	60	4.5913 ± 3.4953	56	5.3450 ± 3.9831			

*Expressed in terms of median (range)

Example 6

Pharmacokinetic data (C_{max}, AUC_(0-t), AUC_(0-∞), and T_{max}) for progesterone, estradiol, free estrone, and total estrone is presented in Tables 14-17. Pharmaceutical com-

positions A-E are disclosed in Tables 1-5. The pK values for pharmaceutical composition E were calculated as disclosed in Example 5. For pharmaceutical compositions A-D, expected pharmacokinetic data is calculated from the data disclosed for pharmaceutical composition E.

TABLE 14

 Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Progesterone

Pharmaceutical Composition	Progesterone Content	Estradiol Content	C _{max} (ng/mL)	AUC _(0-t) (ng · hr/mL)	AUC _(0-∞) (ng · hr/mL)	T _{max} (hr)
A	50 mg	0.25 mg	22.30555	30.0217	32.8454	3.00
B	50 mg	0.50 mg	22.3055	30.0217	32.8454	3.00
C	100 mg	0.50 mg	44.6111	60.0435	65.6909	3.00
D	100 mg	1 mg	44.6111	60.0435	65.6909	3.00
E	200 mg	2 mg	89.2222	120.0869	131.3817	3.00

TABLE 15

 Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Estradiol

Pharmaceutical Composition	Progesterone Content	Estradiol Content	C _{max} (pg/mL)	AUC _(0-t) (pg · hr/mL)	AUC _(0-∞) (pg · hr/mL)	T _{max} (hr)
A	50 mg	0.25 mg	8.0988	175.4667	307.4299	9.00
B	50 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
C	100 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
D	100 mg	1 mg	32.3951	701.8667	1229.7197	9.00
E	200 mg	2 mg	64.7902	1403.7333	2459.4394	9.00

TABLE 16

 Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Free Estrone

Pharmaceutical Composition	Progesterone Content	Estradiol Content	C _{max} (pg/mL)	AUC _(0-t) (pg · hr/mL)	AUC _(0-∞) (pg · hr/mL)	T _{max} (hr)
A	50 mg	0.25 mg	53.3187	1137.0113	1499.3712	5.50
B	50 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
C	100 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
D	100 mg	1 mg	213.2746	4548.0454	5997.4848	5.50
E	200 mg	2 mg	426.5492	9096.0907	11994.9695	5.50

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TABLE 17

 Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions
 of Tables 1-5 for Total Estrone

Pharmaceutical Composition	Progesterone Content	Estradiol Content	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng · hr/mL)	$AUC_{(0-\infty)}$ (ng · hr/mL)	T_{max} (hr)
A	50 mg	0.25 mg	4.4286	25.2191	26.6550	2.50
B	50 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
C	100 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
D	100 mg	1 mg	17.7145	100.8762	106.6201	2.50
E	200 mg	2 mg	35.4289	201.7524	213.2402	2.50

The ranges of expected pK values for each of the pharmaceutical compositions of Tables 1-4 are disclosed in Tables 18-21, respectively.

TABLE 18

pK Ranges for the Pharmaceutical Composition of Table 1 (Pharmaceutical Composition A)			
	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL
Estradiol	6.4790 pg/mL to 10.1235 pg/mL	140.3733 pg · hr/mL to 219.3333 pg · hr/mL	245.9439 pg · hr/mL to 384.2874 pg · hr/mL
Free estrone	42.6549 pg/mL to 66.6483 pg/mL	909.6091 pg · hr/mL to 1421.2642 pg · hr/mL	1199.4970 pg · hr/mL to 1874.2140 pg · hr/mL
Total estrone	3.5429 ng/mL to 5.5358 ng/mL	20.1752 ng · hr/mL to 31.5238 ng · hr/mL	21.3240 ng · hr/mL to 33.3188 ng · hr/mL

TABLE 19

pK Ranges for the Pharmaceutical Composition of Table 2 (Pharmaceutical Composition B)			
	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

TABLE 20

pK Ranges for the Pharmaceutical Composition of Table 3 (Pharmaceutical Composition C)			
	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

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TABLE 21

pK Ranges for the Pharmaceutical Composition of Table 4 (Pharmaceutical Composition D)			
	C _{max}	AUC _(0-t)	AUC _(0-∞)
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	25.9161 pg/mL to 40.4939 pg/mL	561.4933 pg · hr/mL to 877.3333 pg · hr/mL	983.7758 pg · hr/mL to 1537.1496 pg · hr/mL
Free estrone	170.6197 pg/mL to 266.5933 pg/mL	3638.4363 pg · hr/mL to 5685.0567 pg · hr/mL	4797.9878 pg · hr/mL to 7496.8559 pg · hr/mL
Total estrone	14.1716 ng/mL to 22.1431 ng/mL	80.7010 ng · hr/mL to 126.0953 ng · hr/mL	85.2961 ng · hr/mL to 133.2751 ng · hr/mL

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A method of treating a female human patient having vasomotor symptoms associated with estrogen deficiency, the method comprising orally administering to the female human patient in need of treatment thereof with food a capsule comprising a fill material, the fill material consisting of:

- a. a solubilizing agent consisting of:
 - i. about 196 mg of mono- and diglycerides of caprylic and capric acid; and
 - ii. about 3 mg of at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides;
- b. about 1 mg of 17 β -estradiol, wherein at least about 80% of the 17 β -estradiol is solubilized in the solubilizing agent; and
- c. about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized in the solubilizing agent and a second portion of the progesterone is micronized;

wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the entire amount of the 17 β -estradiol and the progesterone in the capsule is present in the solubilizing agent; and wherein the administration of the capsule to the patient produces one or more pharmacokinetic parameters selected from the group consisting of:

- i. an area under the curve (AUC)(0-t) for 17 β -estradiol ranging from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;

ii. a C_{max} for 17 β -estradiol ranging from 25.9161 pg/ml to 40.4939 pg/ml;

iii. an AUC(0-t) for estrone ranging from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;

iv. a C_{max} for estrone ranging from 170.6197 pg/ml to 266.5933 pg/ml;

v. an AUC(0-t) for progesterone ranging from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and

vi. a C_{max} for progesterone ranging from 35.6889 ng/ml to 55.7639 ng/ml.

2. The method of claim 1, wherein the patient has a uterus.

3. The method of claim 1, wherein the administration of the capsule to the patient further produces a T_{max} for progesterone that ranges from 2.4 hr to 3.8 hr or a T_{max} for estrone ranging from 4.4 hr to 6.9 hr.

4. The method of claim 3, wherein the administration of the capsule to the patient produces three or more of the pharmacokinetic parameters.

5. The method of claim 1, wherein the administration of the capsule to the patient produces the following pharmacokinetic parameters:

a. an AUC(0-t) for 17 β -estradiol ranging from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;

b. a C_{max} for 17 β -estradiol ranging from 25.9161 pg/ml to 40.4939 pg/ml;

c. an AUC(0-t) for estrone ranging from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;

d. a C_{max} for estrone ranging from 170.6197 pg/ml to 266.5933 pg/ml; and

e. an AUC(0-t) for progesterone ranging from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml.

6. The method of claim 1, wherein at least about 15% by weight of the progesterone is solubilized in the solubilizing agent, and at least about 50% by weight of the progesterone is micronized.

7. The method of claim 1, wherein up to about 15% by weight of the progesterone is solubilized in the solubilizing agent.

8. The method of claim 1, wherein the micronized progesterone has an X50 particle size of below about 15 microns, an X90 particle size of below about 25 microns, or both.

9. A method of treating a female human patient having vasomotor symptoms associated with estrogen deficiency, the method comprising orally administering to the female human patient in need of treatment thereof with food a capsule comprising a fill material, the fill material comprising:

- a. a solubilizing agent comprising:

- i. about 196 mg of mono- and diglycerides of caprylic and capric acid; and

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- ii. about 3 mg of at least one of lauryl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF or lauroyl polyoxylglycerides;
- b. about 1 mg of 17 β -estradiol, wherein at least about 80% of the 17 β -estradiol is solubilized in the solubilizing agent;
- c. about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized in the solubilizing agent and a second portion of the progesterone is micronized, and wherein up to about 15% by weight of the progesterone is solubilized in the solubilizing agent; wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the entire amount of the 17 β -estradiol and the progesterone in the capsule is present in the solubilizing agent; and wherein the administration of the capsule to the patient produces one or more pharmacokinetic parameters selected from the group consisting of:
 - i. an area under the curve (AUC)(0-t) for 17 β -estradiol ranging from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
 - ii. a Cmax for 17 β -estradiol ranging from 25.9161 pg/ml to 40.4939 pg/ml;
 - iii. an AUC(0-t) for estrone ranging from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;
 - iv. a Cmax for estrone ranging from 170.6197 pg/ml to 266.5933 pg/ml;
 - v. an AUC(0-t) for progesterone ranging from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
 - vi. a Cmax for progesterone ranging from 35.6889 ng/ml to 55.7639 ng/ml.

10 10. The method of claim 9, wherein the patient has a uterus.

11 11. The method of claim 9, wherein the administration of the capsule to the patient further produces a Tmax for progesterone ranging from 2.4 hr to 3.8 hr or a Tmax for estrone ranging from 4.4 hr to 6.9 hr.

12 12. A method of treating a female human patient having vasomotor symptoms associated with estrogen deficiency, the method comprising orally administering to the patient in need of treatment thereof with food a capsule comprising a fill material, the fill material comprising:

- a. a solubilizing agent comprising:
 - i. a medium chain oil, wherein at least about 80% of fatty acid chains present in the oil are C6-C12 and the medium chain oil comprises about 60% to about 85% of the weight of the fill material; and
 - ii. a non-ionic surfactant, wherein the non-ionic surfactant comprises about 0.1% to about 10.0% of the weight of the fill material;
- b. about 1 mg of 17 β -estradiol, wherein at least about 80% of the 17 β -estradiol is solubilized in the solubilizing agent;
- c. about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized in the solubilizing agent and a second portion of the progesterone is micronized;

wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the entire amount of the 17 β -estradiol and the progesterone in the capsule is present in the solubilizing agent; and wherein the administration of the capsule to the patient produces one or more pharmacokinetic parameters selected from the group consisting of:

- i. an area under the curve (AUC)(0-t) for 17 β -estradiol ranging from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- ii. a Cmax for 17 β -estradiol ranging from 25.9161 pg/ml to 40.4939 pg/ml;

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- iii. an AUC(0-t) for estrone ranging from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;
- iv. a Cmax for estrone ranging from 170.6197 pg/ml to 266.5933 pg/ml;

- v. an AUC(0-t) for progesterone ranging from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- vi. a Cmax for progesterone ranging from 35.6889 ng/ml to 55.7639 ng/ml.

13 13. The method of claim 12, wherein the patient has a uterus.

14 14. The method of claim 12, wherein the administration of the capsule to the patient further produces a Tmax for progesterone ranging from 2.4 hr to 3.8 hr or a Tmax for estrone ranging from 4.4 hr to 6.9 hr.

15 15. The method of claim 12, wherein the ratio of the medium chain oil to the non-ionic surfactant is between about 60:1 to about 70:1.

16 16. The method of claim 12, wherein up to about 15% by weight of the progesterone is solubilized in the solubilizing agent.

17 17. A method of treating a female human patient having vasomotor symptoms associated with estrogen deficiency, the method comprising orally administering to the patient in need of treatment thereof with food a capsule comprising a fill material, the fill material comprising:

- a. a solubilizing agent;
- b. about 1 mg of 17 β -estradiol, wherein at least about 80% of the 17 β -estradiol is solubilized in the solubilizing agent, and wherein the 17 β -estradiol comprises about 0.15% to about 0.4% by weight of the fill material;
- c. about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized in the solubilizing agent and a second portion of the progesterone is micronized, wherein up to about 20% by weight of the progesterone is solubilized in the solubilizing agent, and wherein the progesterone comprises about 30% to about 35% by weight of the fill material; and

wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the entire amount of the 17 β -estradiol and the progesterone in the capsule is present in the solubilizing agent; and wherein the administration of the capsule to the patient produces one or more pharmacokinetic parameters selected from the group consisting of:

- i. an area under the curve (AUC)(0-t) for 17 β -estradiol ranging from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- ii. a Cmax for 17 β -estradiol ranging from 25.9161 pg/ml to 40.4939 pg/ml;
- iii. an AUC(0-t) for estrone ranging from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;
- iv. a Cmax for estrone ranging from 170.6197 pg/ml to 266.5933 pg/ml;
- v. an AUC(0-t) for progesterone ranging from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- vi. a Cmax for progesterone ranging from 35.6889 ng/ml to 55.7639 ng/ml.

18 18. The method of claim 17, wherein the patient has a uterus.

19 19. The method of claim 17, wherein the fill material further comprises a surfactant, the surfactant comprising about 0.1% to about 5% by weight of the fill material.

20 20. The method of claim 17, wherein the surfactant is an ionic surfactant, a non-ionic surfactant, or a combination thereof.

21 21. The method of claim 20, wherein the non-ionic surfactant is a medium chain fatty acid ester of polyethylene glycol.

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22. The method of claim **20**, wherein the non-ionic surfactant is a polyethylene glycol glyceride composed of mono-, di-, and triglycerides and mono- and diesters of polyethylene glycol.

23. The method of claim **20**, wherein the non-ionic surfactant is PEG-32 glyceryl laurate EP.

24. The method of claim **20**, wherein the ratio of the solubilizing agent to the non-ionic surfactant is about 65:1.

25. The method of claim **17**, wherein the micronized progesterone has an X50 particle size of below about 15¹⁰ microns, an X90 particle size of below about 25 microns, or both.

26. The method of claim **17**, wherein the solubilizing agent comprises a medium chain oil.

27. The method of claim **26**, wherein the medium chain oil comprises at least about 75% by weight of medium chain fatty acids.

28. The method of claim **19**, wherein the ratio of the solubilizing agent to the surfactant is about 60:1 to about 70:1.

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29. The method of claim **28**, wherein the ratio of the solubilizing agent to the surfactant is about 65:1.

30. The method of claim **17**, wherein up to about 15% by weight of the progesterone is solubilized in the solubilizing agent.

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* * * * *

EXHIBIT Q



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(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 11,103,516 B2
(45) **Date of Patent:** *Aug. 31, 2021

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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This patent is subject to a terminal disclaimer.

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(51) **Int. Cl.**

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(52) **U.S. Cl.**

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CPC .. A61K 2300/00; A61K 31/57; A61K 31/565; A61K 47/14; A61K 9/48; A61K 9/0034; A61K 47/44; A61P 5/24

See application file for complete search history.

(56)

References Cited

U.S. PATENT DOCUMENTS

1,967,351 A	1/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	6/1976	Zaffaroni
3,971,367 A	6/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI1001367-9 A2	7/2012
CA	2044371 A1	12/1991

(Continued)

OTHER PUBLICATIONS

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)
Activella® (estradiol/ norethindrone acetate) prescribing information (Nov. 2017) FDA Label, 39 pages.
Casiero-Brando, C., and Rostro, F., "Treatment of atrophic vaginitis," *Therapy*, 4(3): 349-353, Future Medicine Ltd., London, England (2007).

Center for Drug Evaluation and Research, Application No. NDA 19-781, Clinical Pharmacology and Biopharmaceutics Reviews, 1998, 59 pages, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/19781.cfm.

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

US 11,103,516 B2

Page 2

(56)	References Cited			
U.S. PATENT DOCUMENTS				
4,012,496 A	3/1977 Schopflin et al.	5,595,970 A	1/1997 Garfield et al.	
4,014,334 A	3/1977 Theeuwes et al.	5,605,702 A	2/1997 Teillaud et al.	
4,014,987 A	3/1977 Heller et al.	5,607,691 A	3/1997 Hale et al.	
4,016,251 A	8/1977 Higuchi et al.	5,607,693 A	3/1997 Bonte et al.	
4,071,623 A	1/1978 van der Vies	5,609,617 A	3/1997 Shealy et al.	
4,093,709 A	6/1978 Choi et al.	5,620,705 A	4/1997 Dong et al.	
4,154,820 A	5/1979 Simoons	5,626,866 A	5/1997 Ebert et al.	
4,155,991 A	5/1979 Schopflin et al.	5,629,021 A	5/1997 Wright	
4,196,188 A	4/1980 Besins	5,633,011 A	5/1997 Dong et al.	
4,215,691 A	8/1980 Wong	5,633,242 A	5/1997 Oettel et al.	
4,217,885 A	12/1980 Wong et al.	5,639,743 A	6/1997 Kaswan et al.	
4,310,510 A	1/1982 Sherman et al.	5,645,856 A	7/1997 Lacy et al.	
4,327,725 A	5/1982 Cortese et al.	5,653,983 A	8/1997 Meybeck et al.	
4,372,951 A	2/1983 Vorys	5,656,286 A	8/1997 Miranda et al.	
4,384,096 A	5/1983 Sonnabend	5,660,839 A	8/1997 Allec et al.	
4,393,871 A	7/1983 Vorhauer et al.	5,662,927 A	9/1997 Ehrlich et al.	
4,402,695 A	9/1983 Wong	5,663,160 A	9/1997 Meybeck et al.	
4,423,151 A	12/1983 Baranczuk	5,676,968 A	10/1997 Lipp et al.	
4,449,980 A	5/1984 Millar et al.	5,677,292 A	10/1997 Li et al.	
4,610,687 A	9/1986 Fogwell	5,686,097 A	11/1997 Taskovich et al.	
4,629,449 A	12/1986 Wong	5,693,335 A	12/1997 Xia et al.	
4,732,763 A	3/1988 Beck et al.	5,694,947 A	12/1997 Lehtinen et al.	
4,738,957 A	4/1988 Laurent et al.	5,700,480 A	12/1997 Hille et al.	
4,756,907 A	7/1988 Beck et al.	5,709,844 A	1/1998 Arbeit et al.	
4,762,717 A	8/1988 Crowley, Jr.	5,719,197 A	2/1998 Kanios et al.	
4,788,062 A	11/1988 Gale et al.	5,735,801 A	4/1998 Caillouette	
4,816,257 A	3/1989 Buster et al.	5,739,176 A	4/1998 Dunn et al.	
4,822,616 A	4/1989 Zimmermann et al.	5,744,463 A	4/1998 Bair	
4,865,848 A	9/1989 Cheng et al.	5,747,058 A	5/1998 Tipton et al.	
4,900,734 A	2/1990 Maxson et al.	5,762,614 A	6/1998 Caillouette	
4,906,475 A	3/1990 Kim	5,770,176 A	6/1998 Nargessi	
4,942,158 A	7/1990 Sarpotdar et al.	5,770,219 A	6/1998 Chiang et al.	
4,961,931 A	10/1990 Wong	5,770,220 A	6/1998 Meconi et al.	
5,030,629 A	7/1991 Rajadhyaksha	5,770,227 A	6/1998 Dong et al.	
5,043,331 A	8/1991 Hirvonen et al.	5,776,495 A	7/1998 Duclos et al.	
5,059,426 A	10/1991 Chiang et al.	5,780,044 A	7/1998 Yewey et al.	
5,064,654 A	11/1991 Berner et al.	5,780,050 A	7/1998 Jain et al.	
5,108,995 A	4/1992 Casper	5,788,980 A	8/1998 Nabahi	
5,128,138 A	7/1992 Blank	5,788,984 A	8/1998 Guenther et al.	
5,130,137 A	7/1992 Crowley, Jr.	5,789,442 A	8/1998 Garfield et al.	
5,140,021 A	8/1992 Maxson et al.	5,811,416 A	9/1998 Chwalisz et al.	
5,145,682 A	9/1992 Chien et al.	5,811,547 A	9/1998 Nakamichi et al.	
5,164,416 A	11/1992 Nagai et al.	5,814,329 A	9/1998 Shah	
5,208,225 A	5/1993 Boissonneault et al.	5,820,878 A	10/1998 Hirano et al.	
5,211,952 A	5/1993 Spicer et al.	5,827,200 A	10/1998 Caillouette	
5,252,334 A	10/1993 Chiang et al.	5,840,327 A	11/1998 Gale et al.	
5,280,023 A	1/1994 Ehrlich et al.	5,843,468 A	12/1998 Burkoth et al.	
5,288,496 A	2/1994 Lewis	5,843,979 A	12/1998 Wille et al.	
5,340,584 A	8/1994 Spicer et al.	5,856,603 A	1/1999 Li et al.	
5,340,585 A	8/1994 Pike et al.	5,858,394 A	1/1999 Lipp et al.	
5,340,586 A	8/1994 Pike et al.	5,863,552 A	1/1999 Yue	
5,362,497 A	11/1994 Yamada et al.	5,869,084 A	2/1999 Paradissis et al.	
5,382,573 A	1/1995 Casper	5,882,676 A	3/1999 Lee et al.	
5,393,528 A	2/1995 Staab	5,885,612 A	3/1999 Meconi et al.	
5,393,529 A	2/1995 Hoffmann et al.	5,888,533 A	3/1999 Dunn	
5,419,910 A	5/1995 Lewis	5,891,462 A	4/1999 Carrara	
5,453,279 A	9/1995 Lee et al.	5,891,868 A	4/1999 Cummings et al.	
5,468,736 A	11/1995 Hodgen	5,916,176 A	4/1999 Yaliammalli et al.	
5,474,783 A	12/1995 Miranda et al.	5,902,603 A	5/1999 Chen et al.	
5,480,776 A	1/1996 Dullien	5,904,931 A	5/1999 Lipp et al.	
5,514,673 A	5/1996 Heckenmuller et al.	5,906,830 A	5/1999 Farinas et al.	
5,516,528 A	5/1996 Hughes et al.	5,912,010 A	6/1999 Wille et al.	
5,527,534 A	6/1996 Myhling	5,916,176 A	6/1999 Caillouette	
5,529,782 A	6/1996 Staab	RE36,247 E	7/1999 Plunkett et al.	
5,538,736 A	7/1996 Hoffmann et al.	5,919,477 A	7/1999 Bevan et al.	
5,543,150 A	8/1996 Bologna et al.	5,922,349 A	7/1999 Elliesen et al.	
5,547,948 A	8/1996 Barcomb	5,928,666 A	7/1999 Farinas et al.	
5,556,635 A	9/1996 Istin et al.	5,942,243 A	8/1999 Shah	
5,565,199 A	10/1996 Page et al.	5,942,531 A	8/1999 Diaz et al.	
5,567,831 A	10/1996 Li	5,952,000 A	9/1999 Venkateshwaran et al.	
5,569,652 A	10/1996 Beier et al.	5,958,446 A	9/1999 Miranda et al.	
5,580,572 A	12/1996 Mikler et al.	5,962,445 A	10/1999 Stewart	
5,582,592 A	12/1996 Kendrick	5,968,919 A	10/1999 Samour et al.	
5,585,370 A	12/1996 Casper	5,972,372 A	10/1999 Saleh et al.	
5,595,759 A	1/1997 Wright et al.	5,985,311 A	11/1999 Cordes et al.	
		5,985,850 A	11/1999 Falk et al.	
		5,985,861 A	11/1999 Levine et al.	
		5,989,568 A	11/1999 Breton et al.	
		5,993,856 A	11/1999 Ragavan et al.	

US 11,103,516 B2

Page 3

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,001,846 A	12/1999	Edwards et al.	6,423,039 B1	7/2002	Rathbone et al.	
6,007,835 A	12/1999	Bon Lapillonne et al.	6,423,683 B1	7/2002	Heaton et al.	
6,010,715 A	1/2000	Wick et al.	6,432,438 B1	8/2002	Shukla	
6,013,276 A	1/2000	Math et al.	6,436,633 B1	8/2002	Kreider et al.	
6,022,562 A	2/2000	Autant et al.	6,440,454 B1	8/2002	Santoro et al.	
6,024,974 A	2/2000	Li	6,444,224 B1	9/2002	Rathbone et al.	
6,024,976 A	2/2000	Miranda et al.	6,444,234 B1	9/2002	Kirby et al.	
6,028,057 A	2/2000	Burns	6,451,300 B1	9/2002	Dunlop et al.	
6,030,948 A	2/2000	Mann	6,451,339 B2	9/2002	Patel et al.	
6,039,968 A	3/2000	Nabahi	6,451,779 B1	9/2002	Hesch	
6,040,340 A	3/2000	Chwalisz et al.	6,455,246 B1	9/2002	Howett et al.	
6,056,972 A	5/2000	Hermsmeyer	6,455,517 B1	9/2002	Tanabe et al.	
6,060,077 A	5/2000	Meignant	6,465,004 B1	10/2002	Rossi Montero et al.	
6,068,853 A	5/2000	Giannos et al.	6,465,005 B1	10/2002	Biali et al.	
6,074,625 A	6/2000	Hawthorne et al.	6,465,006 B1	10/2002	Zhang et al.	
6,077,531 A	6/2000	Salin-Drouin	6,468,526 B2	10/2002	Chrisope	
6,080,118 A	6/2000	Blythe	6,469,016 B1	10/2002	Place et al.	
6,083,178 A	7/2000	Caillouette	6,472,434 B1	10/2002	Place et al.	
6,086,916 A	7/2000	Agnus et al.	6,479,232 B1	11/2002	Howett et al.	
6,087,352 A	7/2000	Trout	6,495,160 B2	12/2002	Esposito et al.	
6,090,404 A	7/2000	Meconi et al.	6,500,814 B1	12/2002	Hesch	
6,096,338 A	8/2000	Lacy et al.	6,503,896 B1	1/2003	Tanabe et al.	
6,106,848 A	8/2000	Preuilh et al.	6,511,969 B1	1/2003	Hermsmeyer	
6,117,446 A	9/2000	Place	6,521,250 B2	2/2003	Meconi et al.	
6,117,450 A	9/2000	Dittgen et al.	6,526,980 B1	3/2003	Tracy et al.	
6,124,362 A	9/2000	Bradbury et al.	6,528,094 B1	3/2003	Savoir et al.	
6,133,251 A	10/2000	Dittgen et al.	6,531,149 B1	3/2003	Kirstgen et al.	
6,133,320 A	10/2000	Yallamnalli et al.	6,537,580 B1	3/2003	Savoir	
6,139,868 A	10/2000	Hoffmann	6,538,039 B2	3/2003	Laurent	
6,139,873 A	10/2000	Hughes, Jr. et al.	6,544,196 B2	4/2003	Caillouette	
6,149,935 A	11/2000	Chiang et al.	6,544,553 B1	4/2003	Hsia et al.	
6,153,216 A	11/2000	Cordes et al.	6,548,053 B1	4/2003	Stewart et al.	
6,165,491 A	12/2000	Grasset et al.	6,548,491 B2	4/2003	Tanabe et al.	
6,165,975 A	12/2000	Adams et al.	6,551,611 B2	4/2003	Elliesen et al.	
6,187,323 B1	2/2001	Aiache et al.	6,555,131 B1	4/2003	Wolff et al.	
6,187,339 B1	2/2001	de Haan et al.	6,562,367 B1	5/2003	Wolff et al.	
6,190,331 B1	2/2001	Caillouette	6,562,370 B2	5/2003	Luo et al.	
6,201,072 B1	3/2001	Rathi et al.	6,562,790 B2	5/2003	Chein	
6,217,886 B1	4/2001	Onyuksel et al.	6,569,463 B2	5/2003	Patel et al.	
6,225,297 B1	5/2001	Stockemann et al.	6,583,129 B1	6/2003	Mazer et al.	
6,227,202 B1	5/2001	Matapurkar	6,586,006 B2	7/2003	Roser et al.	
6,228,383 B1	5/2001	Hansen et al.	6,589,549 B2	7/2003	Shih et al.	
6,228,852 B1	5/2001	Shaak	6,593,317 B1	7/2003	de Ziegler et al.	
6,242,509 B1	6/2001	Berger et al.	6,599,519 B1	7/2003	Seo et al.	
6,245,811 B1	6/2001	Horrobin et al.	6,610,325 B1	8/2003	Meignant et al.	
6,262,115 B1	7/2001	Guittard et al.	6,610,652 B2	8/2003	Adams et al.	
6,267,984 B1	7/2001	Beste et al.	6,610,670 B2	8/2003	Bickensfeld et al.	
6,274,165 B1	8/2001	Meconi et al.	6,610,674 B1	8/2003	Schreiber	
6,277,418 B1	8/2001	Markaverich et al.	6,635,274 B1	10/2003	Masiz et al.	
6,283,927 B1	9/2001	Caillouette	6,638,528 B1	10/2003	Kanios	
6,284,263 B1	9/2001	Place	6,653,298 B2	11/2003	Potter et al.	
6,287,588 B1	9/2001	Shih et al.	6,656,929 B1	12/2003	Agnus et al.	
6,287,693 B1	9/2001	Savoir et al.	6,660,726 B2	12/2003	Hill et al.	
6,291,527 B1	9/2001	Giorgetti	6,663,608 B2	12/2003	Rathbone et al.	
6,294,188 B1	9/2001	Ragavan et al.	6,663,895 B2	12/2003	Savoir et al.	
6,294,192 B1	9/2001	Patel et al.	6,664,296 B1	12/2003	Meignant	
6,294,550 B1	9/2001	Place et al.	6,682,757 B1	1/2004	Wright	
6,299,900 B1	10/2001	Reed et al.	6,692,763 B1	2/2004	Cummings et al.	
6,303,132 B1	10/2001	Nelson	6,708,822 B1	3/2004	Muni	
6,303,588 B1	10/2001	Danielov	6,716,454 B2	4/2004	Meignant et al.	
6,306,841 B1	10/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.	
6,306,914 B1	10/2001	de Ziegler et al.	6,737,081 B2	5/2004	Savoir et al.	
6,309,669 B1	10/2001	Setterstrom et al.	6,740,333 B2	5/2004	Beckett et al.	
6,309,848 B1	10/2001	Howett et al.	6,743,448 B2	6/2004	Kryger	
6,312,703 B1	11/2001	Orthoefer	6,743,815 B2	6/2004	Huebner et al.	
6,328,987 B1	12/2001	Marini	6,747,018 B2	6/2004	Tanabe et al.	
6,342,491 B1	1/2002	Dey et al.	6,750,291 B2	6/2004	Kim et al.	
6,344,211 B1	2/2002	Hille	6,756,208 B2	6/2004	Griffin et al.	
6,372,209 B1	4/2002	Chrisope	6,776,164 B2	8/2004	Bunt et al.	
6,372,245 B1	4/2002	Bowman et al.	6,787,152 B2	9/2004	Kirby et al.	
6,372,246 B1	4/2002	Wei et al.	6,805,877 B2	10/2004	Massara et al.	
6,387,390 B1	5/2002	Deaver et al.	6,809,085 B1	10/2004	Elson et al.	
6,402,705 B1	6/2002	Caillouette	6,818,226 B2	11/2004	Reed et al.	
6,416,778 B1	7/2002	Ragavan et al.	6,821,524 B2	11/2004	Marini	
6,420,352 B1	7/2002	Knowles	6,841,716 B1	1/2005	Tsutsumi	
			6,844,334 B2	1/2005	Hill et al.	

US 11,103,516 B2

Page 4

(56)	References Cited				
U.S. PATENT DOCUMENTS					
6,855,703 B1	2/2005	Hill et al.	7,550,142 B2	6/2009	Giles-Komar et al.
6,860,859 B2	3/2005	Mehrotra et al.	7,563,565 B1	7/2009	Matsuo et al.
6,866,865 B2	3/2005	Hsia et al.	7,569,274 B2	8/2009	Besse et al.
6,869,969 B2	3/2005	Huebner et al.	7,572,779 B2	8/2009	AloBl et al.
6,878,518 B2	4/2005	Whitehead	7,572,780 B2	8/2009	Hermsmeyer
6,901,278 B1	5/2005	Notelovitz	7,589,082 B2	9/2009	Savoir et al.
6,905,705 B2	6/2005	Palm et al.	7,671,027 B2	3/2010	Loumaye
6,911,211 B2	6/2005	Eini et al.	7,674,783 B2	3/2010	Hermsmeyer
6,911,438 B2	6/2005	Wright	7,687,281 B2	3/2010	Roth et al.
6,923,988 B2	8/2005	Patel et al.	7,727,720 B2	6/2010	Dhallan
6,924,274 B2	8/2005	Lardy et al.	7,732,408 B2	6/2010	Josephson et al.
6,932,983 B1	8/2005	Straub et al.	7,749,989 B2	7/2010	Hill et al.
6,939,558 B2	9/2005	Massara et al.	7,767,656 B2	8/2010	Shoichet et al.
6,943,021 B2	9/2005	Klausner et al.	7,799,769 B2	9/2010	White et al.
6,958,327 B1	10/2005	Hillisch et al.	7,815,936 B2	10/2010	Hasenzahl et al.
6,960,337 B2	11/2005	Daniels et al.	7,815,949 B2	10/2010	Cohen
6,962,691 B1	11/2005	Lulla et al.	7,829,115 B2	11/2010	Besins et al.
6,962,908 B2	11/2005	AloBl et al.	7,829,116 B2	11/2010	Griswold et al.
6,967,194 B1	11/2005	Matsuo et al.	RE42,012 E	12/2010	Deaver et al.
6,974,569 B2	12/2005	Dunlop et al.	7,850,992 B2	12/2010	Kim et al.
6,977,250 B2	12/2005	Rodriguez	7,853,607 B2	12/2010	Mamchur
6,978,945 B2	12/2005	Wong et al.	7,854,753 B2	12/2010	Kraft et al.
6,987,129 B2	1/2006	Mak et al.	RE42,072 E	1/2011	Deaver et al.
6,995,149 B1	2/2006	Endrikat et al.	7,862,552 B2	1/2011	McIntyre et al.
7,004,321 B1	2/2006	Palm et al.	7,867,990 B2	1/2011	Schultz et al.
7,005,429 B2	2/2006	Dey et al.	7,871,643 B2	1/2011	Lizio et al.
7,011,846 B2	3/2006	Shojaei et al.	7,879,831 B2	2/2011	Wiley
7,018,992 B2	3/2006	Koch et al.	7,884,093 B2	2/2011	Creasy et al.
7,030,104 B2	4/2006	Gray et al.	7,925,519 B2	4/2011	Greene
7,030,157 B2	4/2006	Ke et al.	7,939,104 B2	5/2011	Blrbera et al.
RE39,104 E	5/2006	Duclos et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,074,779 B2	7/2006	Sui et al.	7,943,604 B2	5/2011	Coelingh Beuniuk et al.
7,083,590 B1	8/2006	Bunt et al.	7,945,459 B2	5/2011	Grace et al.
7,091,213 B2	8/2006	Metcalf, III et al.	7,960,368 B2	6/2011	Nickisch et al.
7,094,228 B2	8/2006	Zhang et al.	7,989,436 B2	8/2011	Hill et al.
7,097,853 B1	8/2006	Garbe et al.	7,989,487 B2	8/2011	Welsh et al.
7,101,342 B1	9/2006	Caillouette	8,002,053 B2	9/2011	Mueller et al.
7,105,573 B2	9/2006	Krajcik et al.	8,048,017 B2	11/2011	Xu
7,135,190 B2	11/2006	Piao et al.	8,048,869 B2	11/2011	Bunschoten et al.
7,153,522 B1	12/2006	Ikeura et al.	8,063,030 B2	11/2011	Ellman
7,163,681 B2	1/2007	Giles-Komar et al.	8,071,576 B2	12/2011	Coelingh Bennink et al.
7,163,699 B2	1/2007	Besse	8,071,729 B2	12/2011	Giles-Komar et al.
7,175,850 B2	2/2007	Cevc	8,075,916 B2	12/2011	Song et al.
7,179,799 B2	2/2007	Hill et al.	8,075,917 B2	12/2011	Chung et al.
7,196,074 B2	3/2007	Blye et al.	8,076,317 B2	12/2011	Kulmann
7,198,800 B1	4/2007	Ko	8,076,319 B2	12/2011	Leonard
7,198,801 B2	4/2007	Carrara et al.	8,080,553 B2	12/2011	Keith et al.
7,226,910 B2	6/2007	Wilson et al.	8,088,605 B2	1/2012	Beudet et al.
7,247,625 B2	7/2007	Zhang et al.	8,096,940 B2	1/2012	Josephson
7,250,446 B2	7/2007	Sangita et al.	8,101,209 B2	1/2012	Legrand et al.
7,267,829 B2	9/2007	Kirby et al.	8,101,773 B2	1/2012	Smith et al.
7,300,926 B2	11/2007	Prokai et al.	8,114,152 B2	2/2012	Furst
7,303,763 B2	12/2007	Ho	8,114,434 B2	2/2012	Sasaki et al.
7,317,037 B2	1/2008	Fensome et al.	8,114,442 B2	2/2012	Tucker et al.
7,329,654 B2	2/2008	Kanojia et al.	8,119,741 B2	2/2012	Pavlina
7,335,650 B2	2/2008	Potter et al.	8,121,886 B2	2/2012	Azar
7,374,779 B2	5/2008	Chen et al.	8,124,118 B2	2/2012	Lennernaes et al.
7,378,404 B2	5/2008	Peters et al.	8,124,595 B2	2/2012	Boissonneault
7,381,427 B2	6/2008	Ancira et al.	8,147,561 B2	4/2012	Binmoeller
7,387,789 B2	6/2008	Klose et al.	8,148,546 B2	4/2012	Schuster et al.
7,388,006 B2	6/2008	Schmees et al.	8,158,613 B2	4/2012	Staniforth et al.
7,414,043 B2	8/2008	Kosemund et al.	8,158,614 B2	4/2012	Lambert et al.
7,427,413 B2	9/2008	Savoir et al.	8,163,722 B2	4/2012	Savoir et al.
7,427,609 B2	9/2008	Leonard	8,177,449 B2	5/2012	Biyly et al.
7,429,576 B2	9/2008	Labrie	8,182,833 B2	5/2012	Hermsmeyer
7,431,941 B2	10/2008	Besins et al.	8,187,615 B2	5/2012	Friedman
7,456,159 B2	11/2008	Houze et al.	8,187,640 B2	5/2012	Dunn
7,459,445 B2	12/2008	Hill et al.	8,195,403 B2	6/2012	Ishikawa et al.
7,465,587 B2	12/2008	Imrich	8,202,736 B2	6/2012	Mousa et al.
7,470,433 B2	12/2008	Carrara et al.	8,217,024 B2	7/2012	Ahmed et al.
7,485,666 B2	2/2009	Villanueva et al.	8,221,785 B2	7/2012	Chien
7,497,855 B2	3/2009	Ausiello et al.	8,222,008 B2	7/2012	Thoene
7,498,303 B2	3/2009	Arnold et al.	8,222,237 B2	7/2012	Nickisch et al.
7,534,765 B2	5/2009	Gregg et al.	8,227,454 B2	7/2012	Hill et al.
7,534,780 B2	5/2009	Wyrwa et al.	8,227,509 B2	7/2012	Castro et al.
			8,241,664 B2	8/2012	Dudley et al.

US 11,103,516 B2

Page 5

(56)	References Cited				
U.S. PATENT DOCUMENTS					
8,247,393 B2	8/2012	Ahmed et al.	8,741,336 B2	6/2014	Dipierro et al.
8,257,724 B2	9/2012	Cromack et al.	8,741,373 B2	6/2014	Bromley et al.
8,257,725 B2	9/2012	Cromack et al.	8,753,661 B2	6/2014	Steinmueller Nethl et al.
8,268,352 B2	9/2012	Vaya et al.	8,784,882 B2	7/2014	Mattern
8,268,806 B2	9/2012	Labrie	8,846,648 B2	9/2014	Bernick et al.
8,268,878 B2	9/2012	Armer et al.	8,846,649 B2	9/2014	Bernick et al.
8,273,730 B2	9/2012	Fernandez et al.	8,933,059 B2	1/2015	Bernick et al.
8,287,888 B2	10/2012	Song et al.	8,987,237 B2	3/2015	Bernick et al.
8,288,366 B2	10/2012	Chochinov et al.	8,987,238 B2	3/2015	Bernick et al.
8,318,898 B2	11/2012	Fasel et al.	8,993,548 B2	3/2015	Bernick et al.
8,324,193 B2	12/2012	Lee Sepsick et al.	8,993,549 B2	3/2015	Bernick et al.
8,329,680 B2	12/2012	Evans et al.	9,006,222 B2	4/2015	Bernick et al.
8,337,814 B2	12/2012	Osbakken et al.	9,012,434 B2	4/2015	Bernick et al.
8,344,007 B2	1/2013	Tang et al.	9,114,145 B2	8/2015	Bernick et al.
8,349,820 B2	1/2013	Zeun et al.	9,114,146 B2	8/2015	Bernick et al.
8,353,863 B2	1/2013	Imran	9,180,091 B2	11/2015	Bernick et al.
8,357,723 B2	1/2013	Satyam	9,248,136 B2	2/2016	Bernick et al.
8,361,995 B2	1/2013	Schramm	9,289,382 B2	3/2016	Bernick et al.
8,362,091 B2	1/2013	Tamarinkin et al.	9,301,920 B2	4/2016	Bernick et al.
8,372,424 B2	2/2013	Berry et al.	9,931,349 B2	4/2018	Shadiack et al.
8,372,806 B2	2/2013	Boehler et al.	10,052,386 B2	8/2018	Bernick et al.
8,377,482 B2	2/2013	Laurie et al.	10,098,894 B2	10/2018	Amadio et al.
8,377,994 B2	2/2013	Gray et al.	10,206,932 B2	2/2019	Bernick et al.
8,394,759 B2	3/2013	Barathur et al.	10,258,630 B2	4/2019	Mirkin et al.
8,415,332 B2	4/2013	Diliberti et al.	10,398,708 B2	9/2019	Mirkin et al.
8,420,111 B2	4/2013	Hermsmeyer	10,471,072 B2	11/2019	Bernick et al.
8,435,561 B2	5/2013	Besins et al.	10,537,581 B2	1/2020	Bernick et al.
8,435,972 B2	5/2013	Stein et al.	10,568,891 B2	2/2020	Mirkin et al.
8,449,879 B2	5/2013	Laurent Applegate et al.	10,668,082 B2	6/2020	Mirkin et al.
8,450,108 B2	5/2013	Boyce	10,675,288 B2	6/2020	Bernick et al.
8,454,945 B2	6/2013	McCook et al.	2001/0005728 A1	6/2001	Guittard et al.
8,455,468 B2	6/2013	Hoffman et al.	2001/0009673 A1	7/2001	Lipp et al.
8,461,138 B2	6/2013	Boissonneault	2001/0021816 A1	9/2001	Caillouette
8,476,252 B2	7/2013	Achleitner et al.	2001/0023261 A1	9/2001	Ryoo et al.
8,481,488 B2	7/2013	Carter	2001/0027189 A1	10/2001	Bennink et al.
8,486,374 B2	7/2013	Tamarinkin et al.	2001/0029357 A1	10/2001	Bunt et al.
8,486,442 B2	7/2013	Matsushita et al.	2001/0031747 A1	10/2001	de Ziegler et al.
8,492,368 B2	7/2013	Vanlandingham et al.	2001/0032125 A1	10/2001	Bhan et al.
8,507,467 B2	8/2013	Matsui et al.	2001/0034340 A1	10/2001	Pickar
8,512,693 B2	8/2013	Capito et al.	2001/0053383 A1	12/2001	Miranda et al.
8,512,754 B2	8/2013	Needham	2001/0056068 A1	12/2001	Chwalisz et al.
8,518,376 B2	8/2013	Tamarinkin et al.	2002/0012710 A1	1/2002	Lansky
8,536,159 B2	9/2013	Li et al.	2002/0026158 A1	2/2002	Rathbone et al.
8,540,967 B2	9/2013	Barrett et al.	2002/0028788 A1	3/2002	Bunt et al.
8,541,400 B2	9/2013	Johnsson et al.	2002/0035070 A1	3/2002	Gardlik et al.
8,551,462 B2	10/2013	Goldstein et al.	2002/0058648 A1	5/2002	Hammerly
8,551,508 B2	10/2013	Lee et al.	2002/0058926 A1	5/2002	Rathbone et al.
8,557,281 B2	10/2013	Halliday et al.	2002/0064541 A1	5/2002	Lapidot et al.
8,568,374 B2	10/2013	De Graaff et al.	2002/0076441 A1	6/2002	Shih et al.
8,591,951 B2	11/2013	Kohn et al.	2002/0102308 A1	8/2002	Wei et al.
8,613,951 B2	12/2013	Zale et al.	2002/0107230 A1	8/2002	Waldon et al.
8,633,178 B2	1/2014	Bernick et al.	2002/0114803 A1	8/2002	Deaver et al.
8,633,180 B2	1/2014	Li et al.	2002/0119174 A1	8/2002	Gardlik et al.
8,636,787 B2	1/2014	Sabaria	2002/0119198 A1	8/2002	Gao et al.
8,636,982 B2	1/2014	Tamarinkin et al.	2002/0132801 A1	9/2002	Heil et al.
8,653,129 B2	2/2014	Fein et al.	2002/0137749 A1	9/2002	Levinson et al.
8,658,627 B2	2/2014	Voskuhl	2002/0142017 A1	10/2002	Simonnet
8,658,628 B2	2/2014	Baucom	2002/0151530 A1	10/2002	Leonard et al.
8,663,681 B2	3/2014	Ahmed et al.	2002/0156394 A1	10/2002	Mehrotra et al.
8,663,692 B1	3/2014	Mueller et al.	2002/0169150 A1	11/2002	Pickar
8,663,703 B2	3/2014	Lerner et al.	2002/0169205 A1	11/2002	Chwalisz et al.
8,664,207 B2	3/2014	Li et al.	2002/0173510 A1	11/2002	Levinson et al.
8,669,293 B2	3/2014	Levy et al.	2002/0193356 A1	12/2002	Van Beek et al.
8,679,552 B2	3/2014	Guthery	2002/0193758 A1	12/2002	Sandberg
8,694,358 B2	4/2014	Tryfon	2002/0197286 A1	12/2002	Brandman et al.
8,697,127 B2	4/2014	Sah	2003/0003139 A1	1/2003	Lipp et al.
8,697,710 B2	4/2014	Li et al.	2003/0004145 A1	1/2003	Leonard
8,703,105 B2	4/2014	Tamarinkin et al.	2003/0007994 A1	1/2003	Bunt et al.
8,709,385 B2	4/2014	Tamarinkin et al.	2003/0027772 A1	2/2003	Bretton
8,709,451 B2	4/2014	Nam et al.	2003/0044453 A1	3/2003	Dittgen et al.
8,715,735 B2	5/2014	Funke et al.	2003/0049307 A1	3/2003	Gyurik
8,721,331 B2	5/2014	Raghuprasad	2003/0064097 A1	4/2003	Patel et al.
8,722,021 B2	5/2014	Friedman et al.	2003/0064975 A1	4/2003	Koch et al.
8,734,846 B2	5/2014	Ali et al.	2003/0072760 A1	4/2003	SirBlsku
8,735,381 B2	5/2014	Podolski	2003/0073248 A1	4/2003	Roth et al.

US 11,103,516 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2003/0073673 A1	4/2003	Hesch	2004/0213744 A1	10/2004	Lulla et al.
2003/0077297 A1	4/2003	Chen et al.	2004/0219124 A1	11/2004	Gupta
2003/0078245 A1	4/2003	Bennink et al.	2004/0225140 A1	11/2004	Fernandez et al.
2003/0091620 A1	5/2003	Fikstad et al.	2004/0234606 A1	11/2004	Levine et al.
2003/0091640 A1	5/2003	Ramanathan et al.	2004/0241219 A1	12/2004	Hille et al.
2003/0092691 A1	5/2003	Besse et al.	2004/0243437 A1	12/2004	Grace et al.
2003/0096012 A1	5/2003	Besse et al.	2004/0253319 A1	12/2004	Netke et al.
2003/0104048 A1	6/2003	Patel et al.	2004/0259817 A1	12/2004	Waldon et al.
2003/0109507 A1	6/2003	Franke et al.	2004/0266745 A1	12/2004	Schwanitz et al.
2003/0113268 A1	6/2003	Buenafae et al.	2005/0003003 A1	1/2005	Deaver et al.
2003/0114420 A1	6/2003	Salvati et al.	2005/0004088 A1	1/2005	Hesch
2003/0114430 A1	6/2003	MacLeod et al.	2005/0009428 A1	1/2005	Constantine et al.
2003/0124182 A1	7/2003	Shojaei et al.	2005/0009800 A1	1/2005	Thumbeck et al.
2003/0124191 A1	7/2003	Besse et al.	2005/0014729 A1	1/2005	Pulaski
2003/0130558 A1	7/2003	Massara et al.	2005/0020550 A1	1/2005	Morris et al.
2003/0144258 A1	7/2003	Heil et al.	2005/0020552 A1	1/2005	Aschkenasy et al.
2003/0157157 A1	8/2003	Luo et al.	2005/0021009 A1	1/2005	Massara et al.
2003/0166509 A1	9/2003	Bltycky et al.	2005/0025833 A1	2/2005	Aschkenasy et al.
2003/0170295 A1	9/2003	Kim et al.	2005/0031651 A1	2/2005	Gervais et al.
2003/0175329 A1	9/2003	Azarnoff et al.	2005/0042173 A1	2/2005	Besse et al.
2003/0175333 A1	9/2003	Shefer et al.	2005/0042268 A1	2/2005	Aschkenasy et al.
2003/0180352 A1	9/2003	Patel et al.	2005/0048116 A1	3/2005	Straub et al.
2003/0181353 A1	9/2003	Nyce	2005/0054991 A1	3/2005	Tobyn et al.
2003/0181728 A1	9/2003	Salvati et al.	2005/0079138 A1	4/2005	Chickering, III et al.
2003/0191096 A1	10/2003	Leonard et al.	2005/0085453 A1	4/2005	Govindarajan
2003/0195177 A1	10/2003	Leonard et al.	2005/0101579 A1	5/2005	Shippen
2003/0215496 A1	11/2003	Patel et al.	2005/0113350 A1	5/2005	Duesterberg et al.
2003/0219402 A1	11/2003	Rutter	2005/0118244 A1	6/2005	Theobald et al.
2003/0220297 A1	11/2003	Bernstein et al.	2005/0118272 A1	6/2005	Besse et al.
2003/0224057 A1	12/2003	Martin-Letellier et al.	2005/0129756 A1	6/2005	Podhaisky et al.
2003/0224059 A1	12/2003	Lerner et al.	2005/0152956 A1	7/2005	Dudley
2003/0225047 A1	12/2003	Caubel et al.	2005/0153946 A1	7/2005	Hirsh et al.
2003/0225048 A1	12/2003	Caubel et al.	2005/0164977 A1	7/2005	Coelingh Bennink
2003/0225050 A1	12/2003	Eichardt et al.	2005/0182105 A1	8/2005	Nirschl et al.
2003/0228686 A1	12/2003	Klausner et al.	2005/0186141 A1	8/2005	Gonda et al.
2003/0229057 A1	12/2003	Caubel et al.	2005/0187267 A1	8/2005	Hamann et al.
2003/0235596 A1	12/2003	Gao et al.	2005/0192253 A1	9/2005	Salvati et al.
2003/0236236 A1	12/2003	Chen et al.	2005/0192310 A1	9/2005	Gavai et al.
2004/0009960 A1	1/2004	Heil et al.	2005/0196434 A1	9/2005	Briere
2004/0022820 A1	2/2004	Anderson	2005/0207990 A1	9/2005	Funke et al.
2004/0034001 A1	2/2004	Karara	2005/0209209 A1	9/2005	Koch et al.
2004/0037881 A1	2/2004	Guittard et al.	2005/0214384 A1	9/2005	Juturu et al.
2004/0039356 A1	2/2004	Maki et al.	2005/0220825 A1	10/2005	Funke et al.
2004/0043043 A1	3/2004	Schlyter et al.	2005/0220900 A1	10/2005	Popp et al.
2004/0043943 A1	3/2004	Guittard et al.	2005/0222106 A1	10/2005	Bracht
2004/0044080 A1	3/2004	Place et al.	2005/0228692 A1	10/2005	Hodgdon
2004/0048900 A1	3/2004	Flood	2005/0228718 A1	10/2005	Austin
2004/0052824 A1	3/2004	Abou Chakra-Vernet et al.	2005/0239747 A1	10/2005	Yang et al.
2004/0073024 A1	4/2004	Metcalf, III et al.	2005/0239758 A1	10/2005	Roby
2004/0077605 A1	4/2004	Salvati et al.	2005/0244360 A1	11/2005	Billoni
2004/0077606 A1	4/2004	Salvati et al.	2005/0244522 A1	11/2005	Carrara et al.
2004/0087548 A1	5/2004	Salvati et al.	2005/0245902 A1	11/2005	Cornish et al.
2004/0087564 A1	5/2004	Wright et al.	2005/0250746 A1	11/2005	Iammatteo
2004/0089308 A1	5/2004	Welch	2005/0250750 A1	11/2005	Cummings et al.
2004/0092494 A9	5/2004	Dudley	2005/0250753 A1	11/2005	Fink et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0256028 A1	11/2005	Yun et al.
2004/0093261 A1	5/2004	Jain et al.	2005/0266078 A1	12/2005	Jorda et al.
2004/0097468 A1	5/2004	Wimalawansa	2005/0266088 A1	12/2005	Hinrichs et al.
2004/0101557 A1	5/2004	Gibson et al.	2005/0271597 A1	12/2005	Keith
2004/0106542 A1	6/2004	Deaver et al.	2005/0271598 A1	12/2005	Friedman et al.
2004/0110732 A1	6/2004	Masini Eteve et al.	2005/0272685 A1	12/2005	Hung
2004/0131670 A1	7/2004	Gao	2005/0272712 A1	12/2005	GruB2 et al.
2004/0138103 A1	7/2004	Patt	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0142012 A1	7/2004	Bunt et al.	2006/0018937 A1	1/2006	Friedman et al.
2004/0146539 A1	7/2004	Gupta	2006/0019978 A1	1/2006	Bllog
2004/0146894 A1	7/2004	Warrington et al.	2006/0020002 A1	1/2006	Salvati et al.
2004/0147578 A1	7/2004	Calvet	2006/0030615 A1	2/2006	Fensome et al.
2004/0161435 A1	8/2004	Gupta	2006/0034889 A1	2/2006	Jo et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0034904 A1	2/2006	Weimann
2004/0176336 A1	9/2004	Rodriguez	2006/0040904 A1	2/2006	Ahmed et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0052341 A1	3/2006	Cornish et al.
2004/0191276 A1	9/2004	Muni	2006/0069031 A1	3/2006	Loumaye
2004/0198706 A1	10/2004	Carrara et al.	2006/0078618 A1	4/2006	Constantinides et al.
2004/0210280 A1	10/2004	Liedtke	2006/0083778 A1	4/2006	Allison et al.
			2006/0084704 A1	4/2006	Shih et al.
			2006/0088580 A1	4/2006	Meconi et al.
			2006/0089337 A1	4/2006	Casper et al.
			2006/0093678 A1	5/2006	Chickering, III et al.

US 11,103,516 B2

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(56)

References Cited**U.S. PATENT DOCUMENTS**

2006/0100180 A1	5/2006	Bohlmann et al.	2007/0264349 A1	11/2007	Lee et al.
2006/0106004 A1	5/2006	Brody et al.	2007/0270394 A1	11/2007	El-Alfy et al.
2006/0110415 A1	5/2006	Gupta	2007/0286819 A1	12/2007	DeVries et al.
2006/0111424 A1	5/2006	Salvati et al.	2007/0287688 A1	12/2007	Chan et al.
2006/0121102 A1	6/2006	Chiang	2007/0287789 A1	12/2007	Jones et al.
2006/0121626 A1	6/2006	Imrich	2007/0292359 A1	12/2007	Friedman et al.
2006/0134188 A1	6/2006	Podhaisky et al.	2007/0292387 A1	12/2007	Jon et al.
2006/0135619 A1	6/2006	Kick et al.	2007/0292461 A1	12/2007	Tamarkin et al.
2006/0165744 A1	7/2006	Jamil et al.	2007/0292493 A1	12/2007	Briere
2006/0193789 A1	8/2006	Tamarkin et al.	2007/0298089 A1	12/2007	Saeki et al.
2006/0194775 A1	8/2006	Tofovic et al.	2008/0026035 A1	1/2008	Chollet et al.
2006/0204557 A1	9/2006	Gupta et al.	2008/0026040 A1	1/2008	Farr et al.
2006/0233743 A1	10/2006	Kelly	2008/0026062 A1	1/2008	Farr et al.
2006/0233841 A1	10/2006	Brodbeck et al.	2008/0038219 A1	2/2008	Mosbaugh et al.
2006/0235037 A1	10/2006	Purandare et al.	2008/0038350 A1	2/2008	Gerecke et al.
2006/0240111 A1	10/2006	Fernandez et al.	2008/0039405 A1	2/2008	Langley et al.
2006/0246122 A1	11/2006	Langguth et al.	2008/0050317 A1	2/2008	Tamarkin et al.
2006/0247216 A1	11/2006	Haj-Yehia	2008/0051351 A1	2/2008	Ghisalberti
2006/0247221 A1	11/2006	Coelingh Bennink et al.	2008/0063607 A1	3/2008	Tamarkin et al.
2006/0251581 A1	11/2006	McIntyre et al.	2008/0069779 A1	3/2008	Tamarkin et al.
2006/0252049 A1	11/2006	Shuler et al.	2008/0069791 A1	3/2008	Beissert
2006/0257472 A1	11/2006	Nielsen	2008/0085877 A1	4/2008	Bortz
2006/0275218 A1	12/2006	Tamarkin et al.	2008/0095831 A1	4/2008	McGraw
2006/0275360 A1	12/2006	Ahmed et al.	2008/0095838 A1	4/2008	Abou Chacra-Vernet
2006/0276414 A1	12/2006	Coelingh Bennink et al.	2008/0119537 A1	5/2008	Zhang et al.
2006/0280771 A1	12/2006	Groenewegen et al.	2008/0125402 A1	5/2008	Dilberti
2006/0280797 A1	12/2006	Shoichet et al.	2008/0138379 A1	6/2008	Jennings-Spring
2006/0280800 A1	12/2006	Nagi et al.	2008/0138390 A1	6/2008	Hsu et al.
2006/0292223 A1	12/2006	Woolfson et al.	2008/0139392 A1	6/2008	Acosta Zara et al.
2007/0004693 A1	1/2007	Woolfson et al.	2008/0145423 A1	6/2008	Khan et al.
2007/0004694 A1	1/2007	Woolfson et al.	2008/0153789 A1	6/2008	Dimowski et al.
2007/0009559 A1	1/2007	Li et al.	2008/0175814 A1	7/2008	Phiasivongsa et al.
2007/0009594 A1	1/2007	Constantine et al.	2008/0175905 A1	7/2008	Liu et al.
2007/0010550 A1	1/2007	McKenzie	2008/0175908 A1	7/2008	Liu et al.
2007/0014839 A1	1/2007	Bracht	2008/0188829 A1	8/2008	Creasy
2007/0015698 A1	1/2007	Kleinman et al.	2008/0206156 A1	8/2008	Cronk
2007/0021360 A1	1/2007	Nyce et al.	2008/0206159 A1	8/2008	Tamarkin et al.
2007/0027201 A1	2/2007	McComas et al.	2008/0206161 A1	8/2008	Tamarkin et al.
2007/0031491 A1	2/2007	Levine et al.	2008/0214512 A1	9/2008	Seitz et al.
2007/0036843 A1	2/2007	Hirsh et al.	2008/0220069 A1	9/2008	Allison
2007/0037780 A1	2/2007	Ebert et al.	2008/0226698 A1	9/2008	Tang et al.
2007/0037782 A1	2/2007	Hibino et al.	2008/0227763 A1	9/2008	Lanquetin et al.
2007/0042038 A1	2/2007	Besse	2008/0234199 A1	9/2008	Katamreddy
2007/0049567 A1	3/2007	Wiley	2008/0234240 A1	9/2008	Duesterberg et al.
2007/0060589 A1	3/2007	Purandare et al.	2008/0255078 A1	10/2008	Katamreddy
2007/0066628 A1	3/2007	Zhang et al.	2008/0255089 A1	10/2008	Katamreddy
2007/0066637 A1	3/2007	Zhang et al.	2008/0261931 A1	10/2008	Hedner et al.
2007/0066675 A1	3/2007	Zhang et al.	2008/0113953 A1	12/2008	DeVries et al.
2007/0071777 A1	3/2007	Bromer et al.	2008/0114050 A1	12/2008	Fensome et al.
2007/0078091 A1	4/2007	Hubler et al.	2008/0299220 A1	12/2008	Tamarkin et al.
2007/0088029 A1	4/2007	Bllog et al.	2008/0306036 A1	12/2008	Katamreddy
2007/0093548 A1	4/2007	Diffendal et al.	2008/0312197 A1	12/2008	Rodriguez
2007/0116729 A1	5/2007	Palepu	2008/0312198 A1	12/2008	Rodriguez
2007/0116829 A1	5/2007	Prakash et al.	2008/0319078 A1	12/2008	Katamreddy
2007/0128263 A1	6/2007	Gargiulo et al.	2009/0004246 A1	1/2009	Woolfson et al.
2007/0154533 A1	7/2007	Dudley	2009/0010968 A1	1/2009	Allart et al.
2007/0167418 A1	7/2007	Ferguson	2009/0011041 A1	1/2009	Musaeva et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0017120 A1	1/2009	Trimble et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0022683 A1	1/2009	Song et al.
2007/0185068 A1	8/2007	Ferguson et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0190022 A1	8/2007	Bacopoulos et al.	2009/0053294 A1	2/2009	Prendergast
2007/0191319 A1	8/2007	Ke et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0191321 A1	8/2007	Ahmed et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0196415 A1	8/2007	Chen et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196433 A1	8/2007	Ron et al.	2009/0074859 A1	3/2009	Patel
2007/0207225 A1	9/2007	Squadrito	2009/0081206 A1	3/2009	Leibovitz
2007/0225281 A1	9/2007	Zhang et al.	2009/0081278 A1	3/2009	De Graaff et al.
2007/0232574 A1	10/2007	Galey et al.	2009/0081303 A1	3/2009	Savoir et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0243229 A1	10/2007	Smith et al.	2009/0093440 A1	4/2009	Murad
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0098069 A1	4/2009	Vacca
2007/0254858 A1	11/2007	Cronk	2009/0099106 A1	4/2009	Phiasivongsa et al.
2007/0255197 A1	11/2007	Humberstone et al.	2009/0099149 A1	4/2009	Liu et al.
2007/0264309 A1	11/2007	Chollet et al.	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0264345 A1	11/2007	Eros et al.	2009/0131385 A1	5/2009	Voskuhl
			2009/0136574 A1	5/2009	Diaz-Astruc et al.
			2009/0137478 A1	5/2009	Bernstein et al.
			2009/0137538 A1	5/2009	Klamerus et al.
			2009/0143344 A1	6/2009	Chang

US 11,103,516 B2

Page 8

(56)

References Cited**U.S. PATENT DOCUMENTS**

2009/0164341 A1	6/2009	Sunvold et al.	2011/0130372 A1	6/2011	Agostinacchio et al.
2009/0175799 A1	7/2009	Tamarkin et al.	2011/0135719 A1	6/2011	Besins et al.
2009/0181088 A1	7/2009	Song et al.	2011/0142945 A1	6/2011	Chen et al.
2009/0186081 A1	7/2009	Holm et al.	2011/0152840 A1	6/2011	Lee et al.
2009/0197843 A1	8/2009	Notelovitz et al.	2011/0158920 A1	6/2011	Morley et al.
2009/0203658 A1	8/2009	Marx et al.	2011/0171140 A1	7/2011	Illum et al.
2009/0214474 A1	8/2009	Jennings	2011/0182997 A1	7/2011	Lewis et al.
2009/0227025 A1	9/2009	Nichols et al.	2011/0190201 A1	8/2011	Hyde et al.
2009/0227550 A1	9/2009	Mattern	2011/0195031 A1	8/2011	Du
2009/0232897 A1	9/2009	Sahoo et al.	2011/0238003 A1	9/2011	Bruno Raimondi et al.
2009/0258096 A1	10/2009	Cohen	2011/0244043 A1	10/2011	Xu et al.
2009/0264395 A1	10/2009	Creasy	2011/0250256 A1	10/2011	Hyun Oh et al.
2009/0269403 A1	10/2009	Shaked et al.	2011/0250259 A1	10/2011	Buckman
2009/0285772 A1	11/2009	Phasivongsa et al.	2011/0250274 A1	10/2011	Shaked et al.
2009/0285869 A1	11/2009	Trimble	2011/0256092 A1	10/2011	Phasivongsa et al.
2009/0318558 A1	12/2009	Kim et al.	2011/0262373 A1	10/2011	Umbert Millet
2009/0324714 A1	12/2009	Liu et al.	2011/0262494 A1	10/2011	Achleitner et al.
2009/0325916 A1	12/2009	Zhang et al.	2011/0268665 A1	11/2011	Tamarkin et al.
2010/0008985 A1	1/2010	Pellikaan et al.	2011/0275584 A1	11/2011	Wilckens et al.
2010/0028360 A1	2/2010	Atwood	2011/0281832 A1	11/2011	Li et al.
2010/0034838 A1	2/2010	Staniforth et al.	2011/0287094 A1	11/2011	Penhasi et al.
2010/0034880 A1	2/2010	Sintov et al.	2011/0293720 A1	12/2011	General et al.
2010/0040671 A1	2/2010	Ahmed et al.	2011/0294738 A1	12/2011	Ren et al.
2010/0048523 A1	2/2010	Blchman et al.	2011/0300167 A1	12/2011	McMurry et al.
2010/0055138 A1	3/2010	Margulies et al.	2011/0301087 A1	12/2011	McBride et al.
2010/0074959 A1	3/2010	Hansom et al.	2011/0306579 A1	12/2011	Stein
2010/0086501 A1	4/2010	Chang et al.	2011/0311592 A1	12/2011	BirBla
2010/0086599 A1	4/2010	Huempel et al.	2011/0312927 A1	12/2011	Nachaegari et al.
2010/0092568 A1	4/2010	Lerner et al.	2011/0312928 A1	12/2011	Nachaegari et al.
2010/0105071 A1	4/2010	Laufer et al.	2011/0318405 A1	12/2011	Erwin
2010/0119585 A1	5/2010	Hille et al.	2011/0318431 A1	12/2011	Gulati
2010/0129320 A1	5/2010	Phasivongsa et al.	2012/0009276 A1	1/2012	De Groote
2010/0136105 A1	6/2010	Chen et al.	2012/0015350 A1	1/2012	Nabtianyan et al.
2010/0137265 A1	6/2010	Leonard	2012/0021041 A1	1/2012	Rossi et al.
2010/0137271 A1	6/2010	Chen et al.	2012/0028888 A1	2/2012	Janz et al.
2010/0143420 A1	6/2010	Shenoy et al.	2012/0028910 A1	2/2012	Takruri et al.
2010/0143481 A1	6/2010	Shenoy et al.	2012/0028936 A1	2/2012	Gloge et al.
2010/0150993 A1	6/2010	Theobald et al.	2012/0045532 A1	2/2012	Cohen
2010/0152144 A1	6/2010	Hermsmeyer	2012/0046264 A1	2/2012	Simes et al.
2010/0168228 A1	7/2010	Bose et al.	2012/0046518 A1	2/2012	Yoakum et al.
2010/0183723 A1	7/2010	Laurent-Applegate et al.	2012/0052077 A1	3/2012	Truitt, III et al.
2010/0184736 A1	7/2010	Coelingh Bennink et al.	2012/0058171 A1	3/2012	De Graaff et al.
2010/0190758 A1	7/2010	Fauser et al.	2012/0058962 A1	3/2012	Cumming et al.
2010/0204326 A1	8/2010	D Souza	2012/0058979 A1	3/2012	Keith et al.
2010/0210994 A1	8/2010	Zarif	2012/0064135 A1	3/2012	Levin et al.
2010/0221195 A1	9/2010	Tamarkin et al.	2012/0065179 A1	3/2012	Andersson
2010/0227797 A1	9/2010	Axelson et al.	2012/0065221 A1	3/2012	Bibul
2010/0240626 A1	9/2010	Kulkarni et al.	2012/0087872 A1	4/2012	Tamarkin et al.
2010/0247482 A1	9/2010	Cui et al.	2012/0101073 A1	4/2012	Mannion et al.
2010/0247632 A1	9/2010	Dong et al.	2012/0121517 A1	5/2012	Song et al.
2010/0247635 A1	9/2010	Rosenberg et al.	2012/0121692 A1	5/2012	Xu et al.
2010/0255085 A1	10/2010	Liu et al.	2012/0122829 A1	5/2012	Taravella et al.
2010/0273730 A1	10/2010	Hsu et al.	2012/0128625 A1	5/2012	Shalwitz et al.
2010/0278759 A1	11/2010	Murad	2012/0128654 A1	5/2012	Terpstra et al.
2010/0279988 A1	11/2010	Setiawan et al.	2012/0128683 A1	5/2012	Shantha
2010/0291191 A1	11/2010	Shoichet et al.	2012/0128733 A1	5/2012	Perrin et al.
2010/0292199 A1	11/2010	Leverb et al.	2012/0128777 A1	5/2012	Keck et al.
2010/0303825 A9	12/2010	SirBlsku	2012/0129773 A1	5/2012	Geier et al.
2010/0312137 A1	12/2010	Gilmour et al.	2012/0129819 A1	5/2012	Vancaillie et al.
2010/0316724 A1	12/2010	Whitfield et al.	2012/0136013 A1	5/2012	Li et al.
2010/0322884 A1	12/2010	Dipietro et al.	2012/0142645 A1	6/2012	Marx
2010/0330168 A1	12/2010	Gicquel et al.	2012/0148670 A1	6/2012	Kim et al.
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0149748 A1	6/2012	Shanler et al.
2011/0039814 A1	2/2011	Huatan et al.	2012/0172343 A1	7/2012	Lindenthal et al.
2011/0053845 A1	3/2011	Levine et al.	2012/0184515 A1	7/2012	Klar et al.
2011/0066473 A1	3/2011	Bernick et al.	2012/0231052 A1	9/2012	Sitruk Ware et al.
2011/0076775 A1	3/2011	Stewart et al.	2012/0232011 A1	9/2012	Kneissel et al.
2011/0076776 A1	3/2011	Stewart et al.	2012/0232042 A1	9/2012	Klar et al.
2011/0086825 A1	4/2011	Chatroux	2012/0263679 A1	10/2012	Marlow et al.
2011/0087192 A1	4/2011	Uhland et al.	2012/0269721 A1	10/2012	Weng et al.
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0269878 A2	10/2012	Cantor
2011/0098258 A1	4/2011	Masini Eteve et al.	2012/0277249 A1	11/2012	Andersson et al.
2011/0098631 A1	4/2011	McIntyre et al.	2012/0277727 A1	11/2012	Doshi et al.
2011/0104268 A1	5/2011	Pachot et al.	2012/0283671 A1	11/2012	ShiBla et al.
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	2012/0295911 A1	11/2012	Mannion et al.
			2012/0301517 A1	11/2012	Zhang et al.

US 11,103,516 B2

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(56)

References Cited**U.S. PATENT DOCUMENTS**

2012/0301538 A1	11/2012	Gordon Beresford et al.	2013/0338123 A1	12/2013	Bernick et al.
2012/0302535 A1	11/2012	Caufriez et al.	2013/0338124 A1	12/2013	Li et al.
2012/0316130 A1	12/2012	Hendrix	2013/0345187 A1	12/2013	Rodriguez Oquendo
2012/0316496 A1	12/2012	Hoffmann et al.	2014/0018335 A1	1/2014	Tatani et al.
2012/0321579 A1	12/2012	Edelson et al.	2014/0024590 A1	1/2014	Weidhaas et al.
2012/0322779 A9	12/2012	Voskuhl	2014/0031289 A1	1/2014	Song et al.
2012/0328549 A1	12/2012	Edelson et al.	2014/0031323 A1	1/2014	Perez
2012/0329738 A1	12/2012	Liu	2014/0066416 A1	3/2014	Leunis et al.
2013/0004619 A1	1/2013	Chow et al.	2014/0072531 A1	3/2014	Kim et al.
2013/0011342 A1	1/2013	Tamarkin et al.	2014/0079686 A1	3/2014	Prouty et al.
2013/0017239 A1	1/2013	Viladot Petit et al.	2014/0088051 A1	3/2014	Bernick et al.
2013/0022674 A1	1/2013	Dudley et al.	2014/0088058 A1	3/2014	Maurizio
2013/0023505 A1	1/2013	Garfield et al.	2014/0088059 A1	3/2014	Perumal et al.
2013/0023823 A1	1/2013	Simpson et al.	2014/0094426 A1	4/2014	Drummond et al.
2013/0028850 A1	1/2013	Tamarkin et al.	2014/0094440 A1	4/2014	Bernick et al.
2013/0029947 A1	1/2013	Nachaegari et al.	2014/0094441 A1	4/2014	Bernick et al.
2013/0029957 A1	1/2013	Giliyar et al.	2014/0099362 A1	4/2014	Bernick et al.
2013/0045266 A1	2/2013	Choi et al.	2014/0100159 A1	4/2014	Conrad
2013/0045953 A1	2/2013	Sitruk Ware et al.	2014/0100204 A1	4/2014	Bernick et al.
2013/0059795 A1	3/2013	Lo et al.	2014/0100205 A1	4/2014	Bernick et al.
2013/0064897 A1	3/2013	Binay	2014/0100206 A1	4/2014	Bernick et al.
2013/0072466 A1	3/2013	Choi et al.	2014/0113889 A1	4/2014	Connor et al.
2013/0084257 A1	4/2013	Ishida et al.	2014/0127185 A1	5/2014	Stein et al.
2013/0085123 A1	4/2013	Li et al.	2014/0127280 A1	5/2014	Duesterberg et al.
2013/0089574 A1	4/2013	Schmidt Gollwitzer et al.	2014/0127308 A1	5/2014	Opara et al.
2013/0090318 A1	4/2013	Ullmann et al.	2014/0128798 A1	5/2014	Janson et al.
2013/0102781 A1	4/2013	Bevill et al.	2014/0148491 A1	5/2014	Valia et al.
2013/0108551 A1	5/2013	Langereis et al.	2014/0186332 A1	7/2014	Ezrin et al.
2013/0116215 A1	5/2013	Coma et al.	2014/0187487 A1	7/2014	Shoichet et al.
2013/0116222 A1	5/2013	Arnold et al.	2014/0193523 A1	7/2014	Henry
2013/0122051 A1	5/2013	Abidi et al.	2014/0194396 A1	7/2014	Li et al.
2013/0123175 A1	5/2013	Hill et al.	2014/0206616 A1	7/2014	Ko et al.
2013/0123220 A1	5/2013	Queiroz	2014/0213565 A1	7/2014	Bernick et al.
2013/0123351 A1	5/2013	Dewitt	2014/0329783 A1	11/2014	Bernick et al.
2013/0129818 A1	5/2013	Bernick et al.	2014/0370084 A1	12/2014	Bernick et al.
2013/0131027 A1	5/2013	Pakkalin et al.	2014/0371182 A1	12/2014	Bernick et al.
2013/0131028 A1	5/2013	Snyder et al.	2014/0371183 A1	12/2014	Bernick et al.
2013/0131029 A1	5/2013	Biltussen et al.	2014/0371184 A1	12/2014	Bernick et al.
2013/0149314 A1	6/2013	Bullerdiek et al.	2014/0371185 A1	12/2014	Bernick et al.
2013/0164225 A1	6/2013	Tamarkin et al.	2015/0031654 A1	1/2015	Amadio
2013/0164346 A1	6/2013	Lee et al.	2015/0045335 A1	2/2015	Bernick et al.
2013/0165744 A1	6/2013	Carson et al.	2015/0133421 A1	5/2015	Bernick et al.
2013/0178452 A1	7/2013	King	2015/0148323 A1	5/2015	Bernick et al.
2013/0183254 A1	7/2013	Zhou et al.	2015/0164789 A1	6/2015	Bernick et al.
2013/0183325 A1	7/2013	Bottoni et al.	2015/0224117 A1	8/2015	Bernick et al.
2013/0189193 A1	7/2013	Tamarkin et al.	2015/0224118 A1	8/2015	Bernick et al.
2013/0189196 A1	7/2013	Tamarkin et al.	2015/0297733 A1	10/2015	Oberegger et al.
2013/0189230 A1	7/2013	Shoichet et al.	2015/0302435 A1	10/2015	Bernick et al.
2013/0189368 A1	7/2013	Mosqueira et al.	2015/0342963 A1	12/2015	Bernick et al.
2013/0210709 A1	8/2013	McMurtry et al.	2015/0352126 A1	12/2015	Bernick et al.
2013/0216550 A1	8/2013	Penninger et al.	2015/0359737 A1	12/2015	Bernick et al.
2013/0216596 A1	8/2013	Viladot Petit et al.	2016/0030449 A1	2/2016	Persicaner et al.
2013/0224177 A1	8/2013	Kim et al.	2016/0213685 A1	7/2016	Bernick et al.
2013/0224257 A1	8/2013	Sah et al.	2017/0056418 A1	3/2017	Thorsteinsson et al.
2013/0224268 A1	8/2013	Alam et al.	2017/0216310 A1	8/2017	Mirkin et al.
2013/0224300 A1	8/2013	Maggio	2017/0281645 A1	10/2017	Shadiack et al.
2013/0225412 A1	8/2013	Sardari Lodriche et al.	2017/0281646 A1	10/2017	Inskeep et al.
2013/0225542 A1	8/2013	Poegh et al.	2017/0281647 A1	10/2017	Shadiack et al.
2013/0226113 A1	8/2013	Schumacher et al.	2017/0281776 A1	10/2017	Shadiack et al.
2013/0243696 A1	9/2013	Wang et al.	2018/0161343 A1	6/2018	Mirkin et al.
2013/0245253 A1	9/2013	Marx et al.	2018/0161344 A1	6/2018	Mirkin et al.
2013/0245570 A1	9/2013	Jackson	2018/0161345 A1	6/2018	Bernick et al.
2013/0261096 A1	10/2013	Merian et al.	2018/0221389 A1	8/2018	Amadio et al.
2013/0266645 A1	10/2013	Becker et al.	2018/0280410 A1	10/2018	Amadio et al.
2013/0267485 A1	10/2013	Da Silva Maia Filho	2018/0289723 A1	10/2018	Bernick et al.
2013/0273167 A1	10/2013	Lee et al.	2019/0022107 A1	1/2019	Mirkin et al.
2013/0274211 A1	10/2013	Burman et al.	2019/0046542 A1	2/2019	Bernick et al.
2013/0280213 A1	10/2013	Voskuhl	2019/0070197 A1	3/2019	Amadio et al.
2013/0301274 A1	11/2013	Anderson	2019/0142844 A1	5/2019	Bernick et al.
2013/0316374 A1	11/2013	Penninger et al.	2019/0247401 A1	8/2019	Amadio et al.
2013/0317065 A1	11/2013	Tatani et al.	2019/0314386 A1	10/2019	Bernick et al.
2013/0317315 A1	11/2013	Lu et al.	2019/0343771 A1	11/2019	Mirkin et al.
2013/0324565 A1	12/2013	Li et al.	2019/0343845 A1	11/2019	Bernick et al.
2013/0331363 A1	12/2013	Li et al.	2019/0358243 A1	11/2019	Mirkin et al.
2013/0338122 A1	12/2013	Bernick et al.	2020/0069700 A1	3/2020	Bernick et al.
			2020/0090955 A1	3/2020	Hsu et al.
			2020/0147104 A1	5/2020	Bernick et al.
			2020/0171050 A1	6/2020	Bernick et al.

US 11,103,516 B2

Page 10

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2020/0281938 A1	9/2020	Bernick et al.	WO	2001060325	8/2001	
2020/0281940 A1	9/2020	Bernick et al.	WO	2001087276	11/2001	
2020/0323881 A1	10/2020	Bernick et al.	WO	2001091757 A1	12/2001	
			WO	2002007700	1/2002	
			WO	2002011768	2/2002	
			WO	2002022132	3/2002	
			WO	2002040008	5/2002	
			WO	2002041878	5/2002	
FOREIGN PATENT DOCUMENTS						
CA 2612380	12/2006		WO	2002053131	7/2002	
CN 102258455 A	11/2011		WO	2002078602	10/2002	
EP 0261429 A1	3/1988		WO	2002078604	10/2002	
EP 0275716 A1	7/1988		WO	2003028667	4/2003	
EP 0279977 A2	8/1988		WO	2003041718	5/2003	
EP 0622075 A1	11/1994		WO	2003041741	5/2003	
EP 0750495 B1	1/1997		WO	2003068186	8/2003	
EP 0785211 A1	7/1997		WO	2003077923	9/2003	
EP 0785212 A1	7/1997		WO	2003082254	10/2003	
EP 0811381 A1	12/1997		WO	2003092588	11/2003	
EP 904064 A1	3/1999		WO	2004014397 A1	2/2004	
EP 0813412 B1	12/1999		WO	2004014432	2/2004	
EP 1300152 A1	4/2003		WO	200404017983	3/2004	
EP 1094781 B1	7/2008		WO	20040432897	4/2004	
EP 2191833 A1	6/2010		WO	20040432942 A1	4/2004	
GB 452238 A	8/1936		WO	2004052336	6/2004	
GB 720561 A	12/1954		WO	2004054540	7/2004	
GB 848881 A	9/1960		WO	2004054576 A1	7/2004	
GB 874368 A	8/1961		WO	2004080413	9/2004	
GB 1589946 A	5/1981		WO	2004105694 A2	12/2004	
IN 2005KOL0053	8/2005		WO	2004110402 A1	12/2004	
IN 216026	3/2008		WO	2004110408 A2	12/2004	
IN 244217	11/2010		WO	2005027911	3/2005	
JP H 02-207024 A	8/1990		WO	2005030175	4/2005	
JP H 02-264725 A	10/1990		WO	2005081825	9/2005	
JP H 04-503810 A	7/1992		WO	2005087194	9/2005	
JP H 10-251116 A	9/1998		WO	2005115335	12/2005	
JP H 11-514994 A	12/1999		WO	2005120470	12/2005	
JP 2002510336 A	4/2002		WO	2005120517	12/2005	
JP 2006513182 A	4/2006		WO	20060113369	2/2006	
RU 2155582 C2	9/2000		WO	2006034090	3/2006	
RU 2449796 C2	2/2006		WO	2006036899	4/2006	
RU 2317813 C2	2/2008		WO	2006053172	5/2006	
WO WO 1990010425 A1	9/1990		WO	2006105615	10/2006	
WO 1990011064	10/1990		WO	2006113505	10/2006	
WO 1993017686	9/1993		WO	2006138686	12/2006	
WO 1994022426	10/1994		WO	2006138735	12/2006	
WO WO 1995005807	3/1995		WO	2007045027	4/2007	
WO 1995030409	11/1995		WO	2007076144 A2	7/2007	
WO 1996009826	4/1996		WO	2007103294	9/2007	
WO 1996019975	7/1996		WO	2007120868	10/2007	
WO 1996030000	10/1996		WO	2007123790	11/2007	
WO 1997005491	2/1997		WO	2007124250	11/2007	
WO 1997043989	11/1997		WO	2007144151	12/2007	
WO WO 1997040823 A1	11/1997		WO	2008049516	5/2008	
WO 1998010293	3/1998		WO	2008152444	12/2008	
WO 1998032465	7/1998		WO	2009002542	12/2008	
WO WO 1998041217 A1	9/1998		WO	2009036311	3/2009	
WO 1998015280	11/1998		WO	2009040818	4/2009	
WO 1999022680 A1	5/1999		WO	2009069006	6/2009	
WO 1999032072	7/1999		WO	2009098072	8/2009	
WO 1999039700	8/1999		WO	2009133352	11/2009	
WO 1999042109	8/1999		WO	2010033188	3/2010	
WO 1999043304	9/1999		WO	2010146872	12/2010	
WO 1999048477	9/1999		WO	2011000210	1/2011	
WO 1999053910	10/1999		WO	2011073995	6/2011	
WO WO 1999052528 A1	10/1999		WO	2011120084	10/2011	
WO WO 1999055333 A1	11/1999		WO	2011128336	10/2011	
WO 1999063974	12/1999		WO	2012009778	1/2012	
WO WO 1999062497 A1	12/1999		WO	2012024361	2/2012	
WO 2000001351	1/2000		WO	2012055814 A1	5/2012	
WO 2000006175	2/2000		WO	2012055840 A1	5/2012	
WO 2000038659	6/2000		WO	2012065740	5/2012	
WO 2000045795	8/2000		WO	2012098090 A1	7/2012	
WO 2000050007	8/2000		WO	2012116277 A1	8/2012	
WO 2000059577	10/2000		WO	2012118563 A2	9/2012	
WO 2000076522	12/2000		WO	2012120365 A1	9/2012	
WO 2001037808	5/2001		WO	2012127501 A2	9/2012	
WO 2001054699	8/2001		WO	2012156561 A1	11/2012	

US 11,103,516 B2

Page 11

(56)	References Cited		
FOREIGN PATENT DOCUMENTS			
WO	2012156822	A1	11/2012
WO	2012158483	A2	11/2012
WO	2012166909	A1	12/2012
WO	2012170578	A1	12/2012
WO	2013011501	A1	1/2013
WO	2013025449	A1	2/2013
WO	2013028639	A1	2/2013
WO	2013035101	A1	3/2013
WO	2013044067	A1	3/2013
WO	2013045404	A2	4/2013
WO	2013059285	A1	4/2013
WO	2013063279	A1	5/2013
WO	2013064620	A1	5/2013
WO	2013071281	A1	5/2013
WO	WO 2013078422	A2	5/2013
WO	2013088254		6/2013
WO	2013102665	A1	7/2013
WO	2013106437	A1	7/2013
WO	2013112947	A1	8/2013
WO	2013113690		8/2013
WO	2013124415	A1	8/2013
WO	2013127727	A1	9/2013
WO	2013127728	A1	9/2013
WO	2013144356	A1	10/2013
WO	2013149258	A2	10/2013
WO	2013158454	A2	10/2013
WO	2013170052	A1	11/2013
WO	2013178587	A1	12/2013
WO	2013181449	A1	12/2013
WO	2013192248		12/2013
WO	2013192249		12/2013
WO	2013192250		12/2013
WO	2013192251		12/2013
WO	2014001904	A1	1/2014
WO	2014004424	A1	1/2014
WO	2014009434	A1	1/2014
WO	2014018569	A1	1/2014
WO	2014018570	A1	1/2014
WO	2014018571	A2	1/2014
WO	2014018856	A1	1/2014
WO	2014018932	A2	1/2014
WO	2014031958	A1	2/2014
WO	2014041120	A1	3/2014
WO	2014052792	A1	4/2014
WO	2014056897	A1	4/2014
WO	2014066442	A2	5/2014
WO	2014074846	A1	5/2014
WO	2014076231	A1	5/2014
WO	2014076569	A2	5/2014
WO	2014081598	A1	5/2014
WO	2014086739	A1	6/2014
WO	2014093114	A1	6/2014
WO	2014104784	A1	7/2014
WO	WO 2015179782	A1	11/2015
WO	WO 2016018993	A1	2/2016
OTHER PUBLICATIONS			
Chambin, O and Jannin, V., "Interest of Multifunctional Lipid Excipients: Case of Gelucire® 44/14," <i>Drug Development and Industrial Pharmacy</i> , 31(6):527-534, Informa Healthcare, England (Jul. 2005).			
Cho, Y.A. et al., "Transdermal Delivery of Ketorolac Tromethamine: Effects of Vehicles and Penetration Enhancers," <i>Drug Development and Industrial Pharmacy</i> , 30(6):557-564, Marcel Dekker, Inc., United States (2004).			
Cincinelli, E., et al., "First uterine pass effect" is observed when estradiol is placed in the upper but not lower third of the vagina, <i>Fertility and Sterility</i> , 81(5): 1414-1416, Elsevier Inc., Netherlands (2004).			
Cincinelli, E., "Intravaginal oestrogen and progestin administration: advantages and disadvantages," <i>Best Practices & Research Clinical Obstetrics and Gynecology</i> , 22(2): 391-405, Elsevier, Netherlands (2008).			
Co-pending Application, U.S. Appl. No. 16/833,186 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/833,188 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/833,213 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/834,780 Inventor, Bernick, B.A., filed Mar. 30, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/834,844 Inventor, Bernick, B.A., filed Mar. 30, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/837,929, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/837,933, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/837,937, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/875,030 Inventor, Bernick, B.A., filed May 15, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/885,066 Inventor, Bernick, B.A., filed May 27, 2020 (Not Published).			
Co-pending Application, U.S. Appl. No. 16/885,088 Inventor, Bernick, B.A., filed May 27, 2020 (Not Published).			
Crandall, C, "Vaginal Estrogen Preparations: a Review of Safety and Efficacy for Vaginal Atrophy," <i>Journal of Women's Health</i> , 11(10):857-877, Mary Ann Liebert, Inc, United States, (Dec. 2002).			
Cremer Care, Miglyol ® 810,812 INCI: Caprylic/Capric Triglyceride, Cremer Oleo GmbH & Co. KG, pp. 1-7, available at http://s3.amazonaws.com/petercremerma/products/spec_sheets/159/339/301/original/MIGLYOL_810_812_TDS.pdf?1389204445 , Mar. 2013.			
De Vries, T.P.G.M., et al, Guide to Good Prescribing: A Practical Manual, Essential Medicines and Health Products Information Portal, World Health Organization, Annex 3 ("How to explain the use of some dosage forms"), Checklist 11 ("Vaginal tablet without applicator") available at http://apps.who.int/medicinedocs/en/d/Jwhozip23e/7.3.11.html , 2 pages, 1994.			
Ettinger, B., et al., "Measuring symptom relief in studies of vaginal and vulvar atrophy: the most bothersome symptom approach," <i>Menopause</i> , 15(5): 885-889, The North American Menopause Society, United States (2008).			
Eugster-Hausmann, M., et al., "Minimized estradiol absorption with ultra-low-dose 10 µg 17β-estradiol vaginal tablets," <i>Climacteric</i> , 13:219-227, International Menopause Society, United Kingdom (2010).			
Extended European Search Report for EP Application No. EP 13807188.1, Munich, Germany, dated Nov. 23, 2015, 7 pages.			
Garad S., et al., "Preclinical Development for Suspensions," Chapter 5, A.K. Kulshreshtha et al. (eds.), <i>Pharmaceutical Suspensions: From Formulation Development to Manufacturing</i> , Springer, New York, pp. 127-176 (2010).			
Hitchcock, C. L., et al., "Oral micronized progesterone for vasomotor symptoms—a placebo-controlled randomized trial in healthy postmenopausal women," <i>Menopause: The Journal of the North American Menopause Society</i> , 19(8):886-893, The North American Menopause Society, United States, (2012).			
Holm, R., et al., "Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides," <i>European Journal of Pharmaceutical Sciences</i> 20: 91-97, Elsevier, Netherlands (2003).			
Hosmer, J., et al., "Microemulsions Containing Medium-Chain Glycerides as Transdermal Delivery Systems for Hydrophilic and Hydrophobic Drugs," <i>AAPS PharmSciTech</i> , 10(2): 589-596, American Association of Pharmaceutical Scientists, United States (2009).			
Karande, P., et al., "Enhancement of transdermal drug delivery via synergistic action of chemicals," <i>Biochimica et Biophysica Acta</i> , 1788: 2362-2373, Elsevier, Netherlands (2009).			
Kingsburg, S.A., et al., "Treating dyspareunia caused by vaginal atrophy: a review of treatment options using vaginal estrogen therapy," <i>International Journal of Women's Health</i> , 1:105-111, Dove Medical Press Ltd., United Kingdom (2009).			

US 11,103,516 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- Lopes, L. B., et al., "Enhancement of transdermal delivery of progesterone using medium-chain mono and diglycerides as skin penetration enhancers," *Pharmaceutical Development and Technology*, 14(5): 524-529, Informa UK Ltd., United Kingdom (2009).
- Mac Bride, M.B., et al., "Vulvovaginal Atrophy," *Mayo Clinic Proceedings*, 85(1): 87-94, Mayo Foundation for Medical Education and Research, United States (2010).
- March, C. M. et al., "Roles of Estradiol and Progesterone in Eliciting the Midcycle Luteinizing Hormone and Follicle-Stimulating Hormone Surges," *The Journal of Clinical Endocrinology & Metabolism*, 49(4): 507-513, The Endocrine Society, United States (1979).
- Martelli, M.E., Vaginal Medicine Administration, The Gale Encyclopedia of Nursing and Allied Health, Gale Group, pp. 2542-2543 (2002).
- Mirkin, S., et al., "The Replenish Trial: Evaluating TX-001HR, The First Combination 17 (3-Estradioi/Natural Progesterone Capsule using SYMBODA™ technology), a new option for the treatment of menopausal symptoms," 14th World Congress on Menopause, May 1-4, 2014 in Cancun, Mexico, Therapeutics MD, 1 page.
- Monti, D. et al., "Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin," *International Journal of Pharmaceutics*, 237:209-24, Elsevier, Netherlands (2002).
- Non-Final Office Action dated Dec. 12, 2011 in U.S. Appl. No. 12/561,515, Inventors, Bernick, B.A., dated Sep. 17, 2009, 14 pages.
- Final Office Action dated Oct. 26, 2012 in U.S. Appl. No. 12/561,515, Inventors, Bernick, B.A., dated Sep. 17, 2009, 13 pages.
- Notice of Allowance dated Sep. 11, 2013 in U.S. Appl. No. 12/561,515, Inventors, Bernick, B.A., dated Sep. 17, 2009, 12 pages.
- Non-Final Office Action dated Feb. 1, 2016 in U.S. Appl. No. 14/690,955, Inventors, Bernick, B.A., dated Apr. 20, 2015, 9 pages.
- Non-Final Office Action dated Apr. 2, 2020, in U.S. Appl. No. 16/104,101, Inventors, Bernick, B.A., dated Aug. 16, 2018, 10 pages.
- Non-Final Office Action dated Sep. 18, 2015 in U.S. Appl. No. 14/830,398, Inventors, Bernick, B.A., dated Aug. 19, 2015, 6 pages.
- Final Office Action dated Jan. 22, 2016 in U.S. Appl. No. 14/830,398, Inventors, Bernick, B.A., dated Aug. 19, 2015, 12 pages.
- Final Office Action dated Jan. 3, 2017 in U.S. Appl. No. 14/830,398, Inventors, Bernick, B.A., dated Aug. 19, 2015, 15 pages.
- Non-Final Office Action dated Jul. 14, 2017, 2015 in U.S. Appl. No. 14/830,398, Inventors, Bernick, B.A., dated Aug. 19, 2015, 13 pages.
- Pachman, D.R., et al., "Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions," *International Journal of Women's Health*, Dove Medical Press Ltd., United Kingdom, (2010).
- Pickar, J.H., et al., "Pharmacokinetics of the First Combination 17B-Estradioi/Progesterone Capsule in Clinical Development for Hormone Therapy," Presented at the 24th annual meeting of the North American Menopause Society, Oct. 9-12, 2013 in Dallas, TX, 1 page.
- Potluri, P. and Betageri, G.V., "Mixed-micellar proliposomal systems for enhanced oral delivery of progesterone," *Drug Delivery*, 13(3): 227-232, Taylor & Francis Group, LLC, United Kingdom (2006).
- Prometrium® (progesterone, USP) prescribing information (Jun. 2009) FDA Label, 33 pages.
- Rao, R. et al., "The Affect of Capmul, Labrafil and Transcutol on Progesterone 100 Mg Soft Capsules Bioavailability in Indian Healthy Adult Postmenopausal Female Subjects Under Fasting Conditions," *Bioequivalence & Bioavailability*, 7(2):995-1007, Medwin Publishers, United States (2015).
- Regidor, P., "Progesterone in Peri- and Postmenopause: A Review," *Geburtshilfe Frauenheilkd*, 74(11): 995-1002, Georg Thieme Verlag KG Stuttgart, New York (2014).
- Rioux, J.E., et al, "17 β-Estradiol Vaginal Tablet Versus Conjugated Equine Estrogen Vaginal Cream to Relieve Menopausal Atrophic Vaginitis," *Menopause: The Journal of the North American Menopause Society*, 7(3): 156-161, The North American Menopause Society, United States (2000).
- Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences* 11(3):42-49, NIPER, India (2010).
- Simon, J.A., et al., "The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone," *Fertility and Sterility*, 60(1):26-33, Elsevier for the American Society for Reproductive Medicine, United States (1993).
- Simon, J. A. et al., "A vaginal estradiol softgel capsule, TX-004HR, has negligible to very low systemic absorption of estradiol: Efficacy and pharmacokinetic data review," *Maturitas*, 99: 51-58, Elsevier, Netherlands (2017).
- Sofi, S. H. et al., "Gelucire: A Versatile Formulation Excipient," *IJPPR Human*, 10(3): 55-73, (2017).
- Stefanick, M.L., "Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration," *The American Journal of Medicine* 118(12B): 64S-73S, Elsevier, Netherlands (2005).
- Tang, O.S., et al., "Pharmacokinetics of different routes of administration of misoprostol," *Human Reproduction*, 17(2):332-226, European Society of Human Reproduction and Embryology, Belgium (2002).
- Vagifem® (estradiol vaginal tablets) prescribing information (Nov. 2009) FDA Label, 14 pages.
- Wang, H., et al., "Pharmacokinetics of hard micronized progesterone capsules via vaginal or oral route compared with soft micronized capsules in healthy postmenopausal women: a randomized open-label clinical study," *Drug Des Devel Ther.*, 13: 2475-2482, Dove Medical Press Ltd., United Kingdom (2019).
- Abbas et al., Regression of endometrial implants treated with vitamin D₃ in a rat model of endometriosis, *European J of Pharma*, 715 (2013) 72-75, Elsevier.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Safety Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Acarturk, Fusun, Mucoadhesive Vaginal Drug Delivery System, Recent Patents on Drug Delivery & Formulation, 2009, vol. 3, pp. 193-195.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceutical substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Araya-Sibija et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Araya-Sibija, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-21, 2013, Wiley Period., Inc.
- Araya-Sibija, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.

US 11,103,516 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Araya-Sibija, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibija, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, Menopause: The Journal of the North American Menopause Society, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, Advances in Therapy®, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, Yale J Biology and Medicine, vol. 3.5, Feb. 1963, pp. 329-340.
- Azeem, Adnan et al., Microemulsions as a Surrogate Carrier for Dermal Drug Delivery, Drug Development and Industrial Pharmacy, May 2000, vol. 35, No. 5, pp. 525-547 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/03639040802448646>.
- Azure Pharma, Inc., ELESTRINTM—Estradiol Gel, Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, Aug. 2009.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, Current Medicinal Chemistry, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, Biology of Reproduction 52, 1327-1333 (1995).
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chintico Farmaceutico, vol. 122(1) pp. 20-6, 1983 SciFinder.
- Bhavnani Bhagu R, et al., “Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy,” J Clin Endocrinol Metab, Mar. 2012, 97(3):756-159.
- Bhavnani et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER α and ER β , Endocrinology, Oct. 2008, 149(10):4857-4870.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductive-aged female subjects, Fertility and Sterility® vol. 94, No. 4, Sep. 2010, Elsevier.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index> [Feb. 3, 2014 1:37:50 PM].
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l’Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-ortho-thiolophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H., et al., Structure Cristalline et Molcculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, J Clin Oncol 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, Contact Dermatitis 2008: 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, Contact Dermatitis, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance , Contact Dermatitis, 71, 264-272, 2014.
- Chun et al., Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles . . . , J. Kor. Pharm. Sci., vol. 35, No. 3, pp. 173-177 (2005).
- Cincinelli et al., Direct Transport of Progesterone From Vagina to Uterus, Obstetrics & Gynecology, vol. 95, No. 3, Mar. 2000, pp. 403-406.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Committee Opinion, Incidentally Detected Short Cervical Length, Committee of Obstetric Practice, Obstetrics & Gynecology, ACOG, vol. 119, No. 4, Apr. 2012, pp. 879-882.
- Commodari, Fernando, Comparison of 17 β -estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-4450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Corbett et al., “Trends in Pharmacy Compounding for Women’s Health in North Carolina: Focus on Vulvodynia,” Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Corn Refiners Association, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Critchley et al., Estrogen Receptor β , But Not Estrogen Receptor α , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, The Journal of Clinical Endocrinology & Metabolism, 2001, vol. 86, No. 3, pp. 1370-1378.
- Dauqan, Eqbil M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Diramio, Jackie A., Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs, Masters of Science Thesis, University of Georgia, Athens, Georgia, 2002, 131 pages.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, Menopause: The Journal of the North American Menopause Society, 2013, vol. 20, No. 11, pp. 1-7.

US 11,103,516 B2

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- (56) **References Cited**
- OTHER PUBLICATIONS**
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *SciFinder, Pharmaceutica Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Estradiol, The Merck Index Online, Royal Society of Chemistry, <https://www.rsc.org/Merck-Index/monograph/mono1500003758/estradiol?q=unauthoriz>.
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GMBH, 2010, 28 pages.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplimentceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Brazil.
- Filipsson al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene Based on exposure and effect data, *Contact Dermatitis* 1990; 23: 341-345.
- Fotherby, K., Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, *Contraception*, 1996; 54:59-69.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Fuchs et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Cutis*. Jun. 2003;71(6):481-8.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gäfvert el. al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Ganam-Quintana et al., Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss, *International Journal of Pharmaceutics*, vo. 147, No. 2, Feb. 28, 1997, pp. 165-171 (abstract only).
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/B1ck-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medinin-chain dity acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Giron-Forest, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Glaser et al., Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al., Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Gunstone, Frank D, et al, Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Gurney, E.P. et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J.Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- Haner, Barbara, Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hargrove et al., Menopausal Hormone Replacement with Continuous Daily Oral Micronize Estradiol and Progesterone, *Obstet Gynecol*, vol. 73, No. 4, Apr. 1989, pp. 606-612.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helbeing, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Sturdy of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.

US 11,103,516 B2

Page 15

(56)

References Cited

OTHER PUBLICATIONS

- Herman, Anna et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, Journal of Pharmacy and Pharmacology, pp. 1-13.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hospital, Michel, et al, X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hostynk, JJ, Predicting absorption of fragrance chemicals through human skin, J. Soc. Cosmet. Chem. 46, 221-229 (Jul./Aug. 1995).
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Humberstone, Andrew et al., "Lipid-based vehicles for the oral delivery of poorly water soluble drugs," Advanced Drug Delivery Reviews, 25 (1997) 103-128.
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, Journal of Cerebral Blood Flow and Metabolism 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 α -Ethyn Estradiol Induces Patterns of Uterine Gene Expression Similar to Endogenous Estrogen 17 β -Estradiol, JPET 290(2):740-747, 1999.
- Idder, Sanna, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johanson, Gunnar, Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester, Critical Reviews in Toxicology, 2000, vol. 30, No. 3, pp. 307-345 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/10408440091159220>.
- Johnson, William S. et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, J Reprod Fert (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, Environmental Health Perspectives • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, Contact Dermatitis, 1992; 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, Ann. Occup. Hyg., vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, Menopause: The Journal of The North American Menopause Society, 2014, vol. 21, No. 6, pp. 1-3.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 100) pp. 771-787, 1984, Marcel Dekker.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, Endocrinology 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation And Risk Assessment of d-Limonene, Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Kincl, et al., Increasing Oral Bioavailability of Progesterone by Formulation, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.
- Knuth et al., Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations, Advanced Drug Delivery Reviews, vol. 11, No. 1-2, Jul.-Aug. 1993, pp. 137-167 (abstract only).
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, European Journal of Pharmaceutics and Biopharmaceutics 64 (2006) 82-91.
- Komm et al., Bazedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, Endocrinology 146(9):3999-4008, 2005.
- Korkmaz, Filiz, Hypophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of The Middle East Tech. University, Sep. 2003
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzymiński, R, et al., EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier (abstract only).
- Kuhnert-Brandstaetter and Grimm, Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II, Mikrochimica Acta, vol. 1, pp. 127-139, 1968.
- Kuhnert-Brandstaetter and Junger and Kofler, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, Microchemical Journal 9, pp. 105-133, 1965.
- Kuhnert-Brandstaetter and Kofler, Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, Mikrochimica Acta, vol. 6, pp. 847-853, 1959.
- Kuhnert-Brandstaetter and Linder, Zur Hydratbildung bei Steroidhormonen, Sci. Pharm, vol. 41(2), pp. 109-116, 1973.
- Kumasaka et al., Effects of Various Forms of Progesterin on the the Estrogen-Primed, Ovariectomized Rat, Endocrine Journal 1994, 41(2), 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, Am J Obstet Gynecol. Jul. 2011; 205(1): e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, FVV in OB/GYN, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, Am J Obstet Gynecol. May 2010 ; 202(5): 455.e1-455.e9.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, Journal of Steroid Biochemistry & Molecular Biology, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Lahiani-Skibl, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W. et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , Jour. of Pharm. Sci., vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, Pharmaceutical Research, vol. 22(5) May 2005, Springer Science+Business Media.
- Lane, Majella E., "Skin penetration enhancers," International Journal of Pharmaceutics 447 (2013) 12-21.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, Alternative Therapies, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.

US 11,103,516 B2

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(56)

References Cited

OTHER PUBLICATIONS

- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G, et al., Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women, *Maturitas*, The European Menopause Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17 α - and 17 β -estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lindmark, Tuulikki et al., "Absorption Enhancement through Intracellular Regulation of Tight Junction Permeability by Medium Chain Fatty Acids in Caco-2 Cells," *JPET* 284(1):362-369, 1998.
- Lindmark, Tuulikki et al., "Mechanisms of Absorption Enhancement by Medium Chain Fatty Acids in Intestinal Epithelial Caco-2 Cell Monolayers," *JPET* 275(2):958-964, 1995.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Lucy et al., Gonadotropin-releasing hormone at estrus: lutenizing horrnone, estradiol, and progesterone during . . . *Biol Reprod* Sep. 1986;35(2):300-311 (abstract only).
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Madishetti et al., Development of domperidone bilayered matrix type trarisdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Magness, R.R., et al., Estrone, Estradiol-17 β and Progesterone Concentrations in Uterine Lymph and Systematic Blood throughout the Porcine Estrone Estrous Cycle, *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- Manson, JoAnn E, et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststoping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- McGuffey, Irena, Softgel Technology as a Lipid-Blsed Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone administration bv'Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Mueck, A.O. et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol.Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Ng, Jo-Han et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*,35(9) pp. 1035, 2009.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia*, vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- NuGen, What is NuGen HP Hair Growth System. NuGest900, NuGest 900™.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical application of pregersterone cream to pre-and post-menopausal women, *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Opinion on the Diethylene Glycol Momoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Panay et al., The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy, *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Panchangnula et al., Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol . . . , *J Pharm Pharmacol*, Sep. 1991;43(9):609-614 (abstract only).
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Intn'l Union ofCrystallography, ISSN 0108-2701, 2003.
- Patel et al., Transdermal Drug Delivery System: A Review, www.thepharmajournal.com, vol. 1, No. 4, 2012, pp. 78-87.
- Payne, R.S., et al., Examples of successfhl crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of The North American Menopause Society*, vol. 21, No. 12, 2014,pp. 1-3.
- Pinkerton, J.-V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gesia L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Position Statement, Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society (NAMS), *Menopause*, vol. 20, No. 9, pp. 888-902.

US 11,103,516 B2

Page 17

(56)

References Cited

OTHER PUBLICATIONS

- Practice Bulletin No. 141, Management of Menopausal Symptoms, Obstetrics & Gynecology, ACOG, vol. 123, No. 1, Jan. 2014, pp. 202-216.
- Prajapati Hetal N. et al., "A Comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water Phase Diagram, Solubility Determination in Dispersion Testing for Application in Pharmaceutical Dosage Form Development," Pharm Res. Jan. 2012; 29(1): 285-305. Published online Aug. 23, 2011, doi: 10.1007/s11095-011-0541-3.
- Prajapati Hetal N. et al., "Effect of Difference in Fatty Acid Chain Lengths of Medium-Chain Lipids on Lipid/Surfactant/Water Phase Diagrams and Drug Solubility," J. Excipients and Food Chem. 2 (3) 2011:73-88.
- Prajapati, Hetal N. et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Prausnitz et al., Transdermal drug delivery, Nat Biotechnol. Nov. 2008 ; 26(11): 1261-1268.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, Adv. Drug Delivery Reviews, vol. 56 pp. 301-319, 2004, Elsevier.
- Product Information Sheet, Body Billance Cream, Tahitian Noni International, 2013, 1 page.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Progesterone, The Merck Index Online, Royal Society of Chemistry, 2013, search Feb. 17, 2014 https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?i=authorize.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause A Systematic Review, Obstet Gynecol 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," J Bioequiv Availab. 2014, 6: 139-143.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, Radiation Research 181, 512-520 (2014).
- Rosilio, V. et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, Pharmaceutical Research, vol. 15(5) pp. 794-799,1998, Plenum Pub. Corp.
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, Ann J Obstet Gynecol, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? Maturitas 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, International Journal of Nanomedicine 2010;5 943-954, Dove Press.
- Sallee, Verney L. et al., "Determinants of intestinal mucosal uptake of short- and medium-chain fatty acids and alcohols," Journal of Lipid Research, 1973, vol. 14, 475-484.
- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Salole, Eugene G., The physicochemical properties of oestradiol, Journal of Pharmaceutical & Biomedical Analysis, vol. 5, No. 7, pp. 635-648, 1987.
- Santen, R.J., Menopausal hormone therapy and breast cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, Climacteric 2014;17:1-14.
- Sarkar, Blsu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Blse . . . , J Steroids Horm Sci, 4:2, 2013.
- Sarpal, K. et al., "Self emulsifying drug delivery systems: a strategy to improve oral bioavailability," Current Research & Information on Pharmaceuticals Sciences (CRIPS), 2010, vol. 11, No. 3, pp. 42-49.
- Sarrel, et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, American Journal of Public Health, Research and Practice, e1-e6. Published online ahead of print Jul. 18, 2013.
- Satyanarayana, D. et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, Asian J. Chem., vol. 9 (3) pp. 418-26, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), J. Steroid Biochem.Mol. Biol. (2013), Elsevier.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, Maturitas 4651 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, Fertil Steril. Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, Toxicologic Pathology, 42: 1188-1196, 2014.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Search Report, Extended European Search Report for EP13741053. 6, dated Jul. 1, 2015.
- Search Report, International Search Report for PCT/US12/66406, dated Jan. 24, 2013.
- Search Report, International Search Report for PCT/US13/23309, dated Apr. 9, 2013.
- Search Report, International Search Report for PCT/US13/46442, dated Nov. 1, 2013.
- Search Report, International Search Report for PCT/US13/46443, dated Oct. 31, 2013.
- Search Report, International Search Report for PCT/US13/46444, dated Oct. 31, 2013.
- Search Report, International Search Report for PCT/US13/46445, dated Nov. 1, 2013.
- Search Report, International Search Report for PCT/US14/61811, dated Jan. 21, 2015.
- Search Report, International Search Report for PCT/US15/23041, dated Jun. 30, 2015.
- Search Report, International Search Report for PCT/US15/042621, dated Oct. 29, 2015.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS DataBise.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, Journal of Experimental & Clinical Cancer Research 2014, 33(1):41, 11 pages.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
- Shufelt et al., Hormone therapy dose, formulation, route delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, Menopause: The Journal of The North American Menopause Society, vol. 21 No. 3, 2014, pp. 1-7, 2013.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Blsed Drug-Delivery Systems, Pharmaceutical Technology, Aug. 2014, pp. 28, 30-31.

US 11,103,516 B2

Page 18

(56)

References Cited

OTHER PUBLICATIONS

- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmapelridch.com/catalog/products/sigma/p7556>.
- Simon et al., Effective Treatment of Vaginal atrophy with art Ultra-low-dose estradiol vaginal tablet, *Obstetrics & Gynecology*, vol. 112, No. 5, Nov. 2008, pp. 1053-1060.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware et al., Progestogens in hormonal replacement therapy: new molecules, risks, and benefits, *Menopause: The Journal of the North American Menopause Society*, vol. 9, No. 1, pp. 6-15, 2002.
- Sitruk-Ware, Regime, "Pharmacological profile of progestins," *Maturitas* 47 (2004) 277-283.
- Sitruk-Ware, Regine, Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review, *Contraception*, Oct. 1987, vol. 36, No. 4, pp. 373-402.
- Smith et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, *JAMA Internal Medicine*, Published online Sep. 30, 2013, E1-E7. jamainternalmedicine.com.
- Smyth et al., Summary of Toxicological Data, A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats, *Fd Cosmet. Toxicol.* vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Therapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, *Contraception*, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause: The Journal of The North American Menopause Society*, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z. et al., Ethynodiol and 17 β -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, *Contraception* 87 (Jun. 2013) vol. 87, No. 6, pp. 706-727.
- Stanczyk, F.Z., "All progestins are not created equal," *Steroids* 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" *Climacteric* 2014;17 (Suppl 2):8-11.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," *Int J Pharmaceutical Compounding*, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Strickley, Robert T., Solubilizing excipients in oral and injectable formulations, *Pharmaceutical Research* Feb. 2004, vol. 21, Issue 2, pp. 201-230 (abstract only).
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- Struhar, M. et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, *Alternative Medicine Review* vol. 12, No. 3, 2007, pp. 259-264.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helveticae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, *Biology of Reproduction* 31, 399-413 (1984).
- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, *Gynecol Endocrinol*, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Thomas, Peter, Characteristics of membrane progestin receptor alpha (mPR α) and progesterone membrane receptor component 1 (PGMRC1) and their roles in mediating rapid progestin actions, *Frontiers in Neuroendocrinology* 29 (2008) 292-312.
- Tripathi, R. et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010.
- Trommer et al., Overcoming the stratum Corneum: The modulation of Skin Penetration, *Skin Pharmacol Physiol* 2006;19:106-121.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- Ueda et al., Topical and Transdermal Drug Products, *Pharmacopeial Forum*, vol. 35(3) [May-Jun. 2009], 750-754.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29024s0_m69870.html, search done: Feb. 25, 2014.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Laupoyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- U.S. Appl. No. 13/843,428 Jul. 2, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/106,655 Jun. 19, 2015 Final Office Action.
- U.S. Appl. No. 13/684,002 Mar. 20, 2013 Non-Final Office Action.
- U.S. Appl. No. 13/684,002 Jul. 16, 2013 Final Office Action.
- U.S. Appl. No. 13/684,002 Dec. 6, 2013 Notice of Allowance.
- U.S. Appl. No. 13/843,362 Mar. 16, 2015 Restriction Requirement.
- U.S. Appl. No. 13/843,428 Apr. 14, 2015 Restriction Requirement.
- U.S. Appl. No. 14/099,545 Feb. 18, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,545 Jul. 14, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,562 Feb. 20, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,562 Mar. 27, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,562 Jul. 2, 2014 Final Office Action.
- U.S. Appl. No. 14/099,562 Dec. 10, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,571 Mar. 28, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,571 Jul. 15, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,582 Apr. 29, 2014 Restriction Requirement.

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(56)

References Cited

OTHER PUBLICATIONS

- U.S. Appl. No. 14/099,582_Jun. 17, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,582_Nov. 7, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,582_Jan. 22, 2015_Notice_of_Allowance.
 U.S. Appl. No. 14/099,598_May 13, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,598_Jul. 3, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,598_Dec. 10, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,612_Mar. 20, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,612_Oct. 30, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,612_Nov. 26, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/099,623_Mar. 5, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/099,623_Jul. 18, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/099,623_Dec. 15, 2014_Notice_of_Allowance.
 U.S. Appl. No. 14/106,655_Jul. 3, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/106,655_Dec. 8, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/125,554_Dec. 5, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/125,554_Apr 14, 2015_Non-Final_Office_Action.
 U.S. Appl. No. 14/136,048_Nov. 4, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/136,048_Mar. 12, 2015_Non-Final_Office_Action.
 U.S. Appl. No. 14/475,814_Oct. 1, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/475,814_Feb. 13, 2015_Notice_of_Allowance.
 U.S. Appl. No. 14/475,864_Oct. 2, 2014_Non-Final_Office_Action.
 U.S. Appl. No. 14/475,864_Feb. 11, 2015_Notice_of_Allowance.
 U.S. Appl. No. 14/476,040_Mar. 26, 2015_Restriction_Requirement.
 U.S. Appl. No. 14/521,230_Dec. 5, 2014_Restriction_Requirement.
 U.S. Appl. No. 14/521,230_Feb. 18, 2015_Non-Final_Office_Action.
 U.S. Appl. No. 14/624,051_Apr. 7, 2015_Non-Final_Office_Action.
 Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens, Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
 Voegtlle et al., Dispatches from the interface of salivary bioscience and neonatal research, Frontiers in Endocrinology, Mar. 2014, vol. 5, article 25, 8 pages.
 Waddell et al., Distribution and metabolism of topically applied progesterone in model, Journal of Steroid Biochemistry & Molecular Biology 80 (2002) 449-455.
 Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role for the Lung, Biology of Reproduction 40, 1188-1193 (1989).
 Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, Reproduction (2005) 129 765-777.
 Weber, E.J., Corn Lipids, Cereal Chem., vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
 Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
 Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," Forbes, Feb. 20, 2015; retrieved online at <http://onforb.es/1LIUmIV> on Feb. 23, 2015, 3 pages.
 Whitehead et al., Absorption and metabolism of oral progesterone, The British Medical Journal, vol. 280, No. 6217 (Mar. 22, 1980), pp. 825-827, BMJ Publishing Group.
 Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
 Wood et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, Breast Cancer Res Treat (2007) 101:125-134.
 Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, Climacteric, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130006500109>.
 Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment the Rat Uterus, Biology of Reproduction 69, 1308-1317 (2003).
 Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
 Yalkowsky, Samuel H, Handbook of Acqueous Solubility Data, Solutions, 2003, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
 Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
 Zava, David T. et al., Percutaneous absorption of progesterone, Maturitas 77 (2014) 91-92, Elsevier.
 Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid.

Non-Final Office Action dated Nov. 13, 2020 in U.S. Appl. No. 16/104,101, Inventors, Bernick, B.A., dated Aug. 16, 2018, 13 pages.

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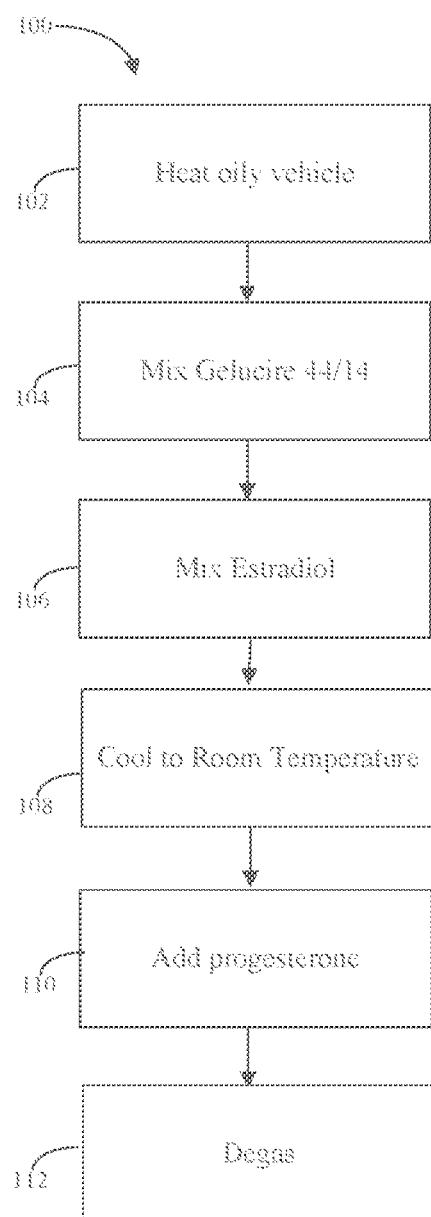
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Fig. 1

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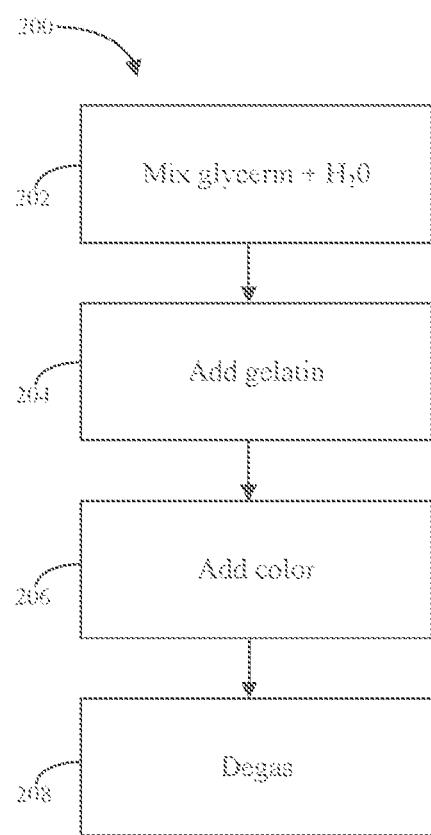


Fig. 2

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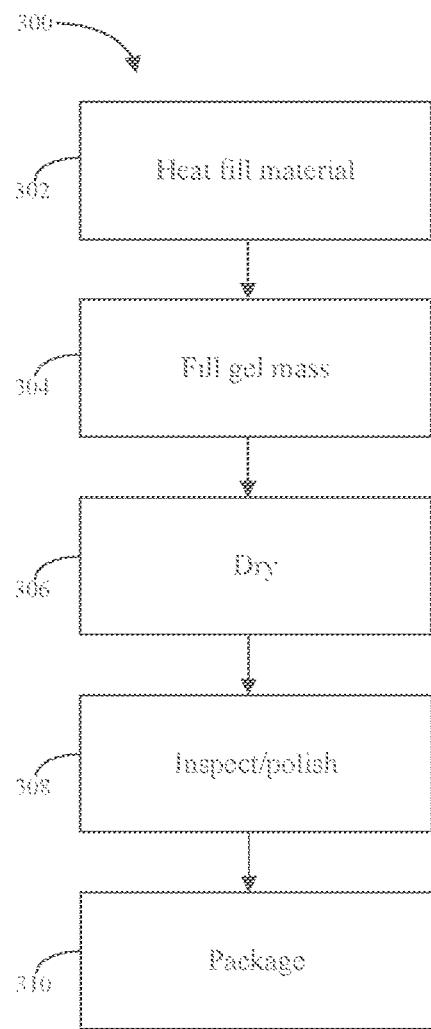


Fig. 3

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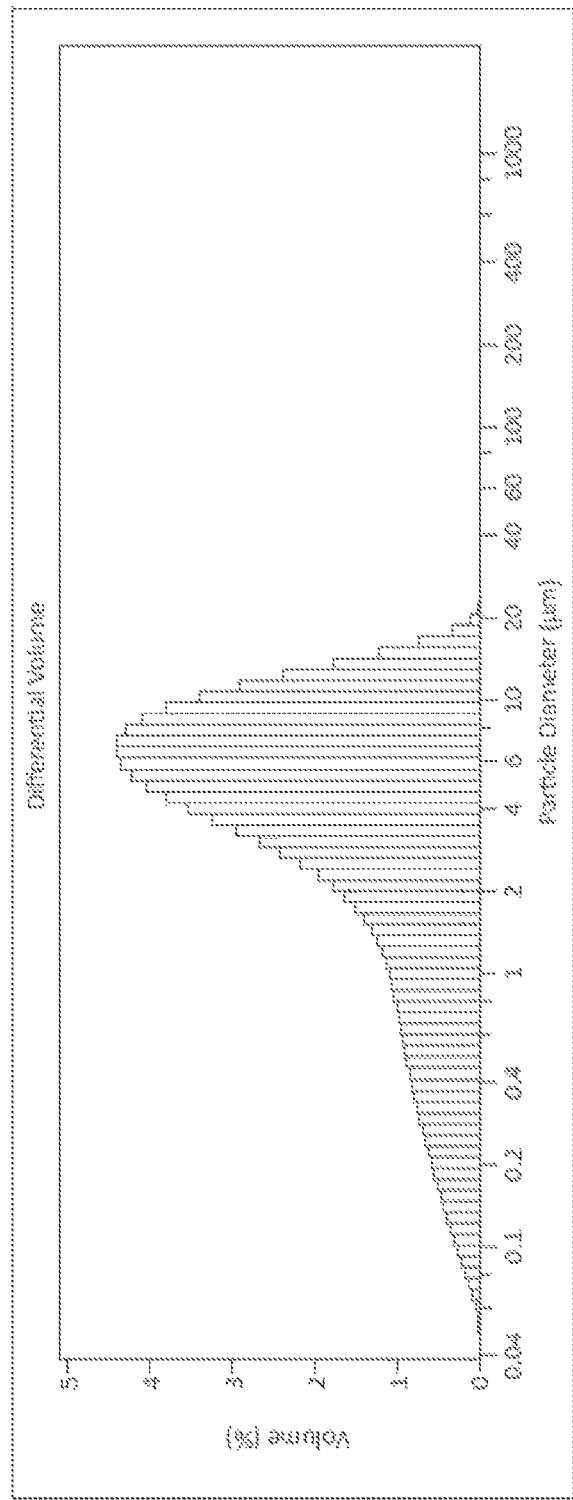


FIG. 3

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCES TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/830,398, filed Aug. 19, 2015, which is a divisional of U.S. patent application Ser. No. 14/476,040, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed on Sep. 3, 2014, which application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for

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approximately two weeks of every month; a method often referred to as "Cyclic-Sequental" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

SUMMARY OF THE INVENTION

According to various embodiments of the disclosure; natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description; further

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serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

A. Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (ply) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, C_{max} , and optionally, Tmax.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ C_{max} ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

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The term, “T_{max}” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

B. Description and Preferred Embodiments

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone; micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to

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the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg; from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg, to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg; and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability; are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively; "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans; having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulva-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylac-

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tically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μ m to 2000 μ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 mg may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propylanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids.

Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

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The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 µm to 2000 µm. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a capric fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®, GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Capmul MCM and Gelucire can be used at ratios

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including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein; and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glycerol mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include; for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids; for example; lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various

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embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally; progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of

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use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2 It can be seen from these results that mixtures containing Miglyol:Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PGS (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol:Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol

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recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG-8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	200
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 2
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total	100	3.25 kg	

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

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Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg, to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Myglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MGM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MGM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM: Gelucire 44/14 (9:1)	86.4
Capmul MCM: Gelucire 44/14 (7:3)	70.5
Capmul MCM: Gelucire 44/14 (6:4)	57.4

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Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm,

the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

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Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MINI, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

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Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

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TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:				100.00	700.00
					7.00

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An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

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Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Clelucire 44/14 NF		1.500	3.00	30.00
Total:				100.00	200.00 mg 2000.00

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The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and

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dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
	Total:	100.00	600.0 mg	6000.0	

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit anchor its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

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Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL, of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL, of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C.±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

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Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C. \pm 5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C. \pm 3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C. \pm 10° C. The wedge temperature may be 38° C. \pm 3° C. The drum cooling temperature may be 4° C. \pm 2° C. The encapsulator may be lubricated using MIGLYOL, 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm \pm 0.05 mm using spreader box knobs. The

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fill material may be injected into the gel to produce a fill weight having target weight \pm 5% (i.e., 650 \pm 33 mg and 325 \pm 16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical composition comprising: a fill material encapsulated in a capsule, the fill material comprising:

- a. two active pharmaceutical ingredients, the active pharmaceutical ingredients being about 1 mg of 17 β -estradiol and about 100 mg of progesterone, wherein at least about 90% of the 17 β -estradiol is solubilized, and wherein a first portion of the progesterone is solubilized and a second portion of the progesterone is micronized;
- b. a solubilizing agent for the active pharmaceutical ingredients, the solubilizing agent comprising:

- i. a medium chain oil comprising mono- and diglycerides of capric and caprylic acid; and
- ii. at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides;

wherein the 17 β -estradiol and the progesterone in the capsule are present in the solubilizing agent; wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; and wherein the progesterone has a solubility in the solubilizing agent of at least about 73 mg/g, and the 17 β -estradiol has a solubility in the solubilizing agent of at least about 10 mg/g.

2. The pharmaceutical composition of claim 1, wherein the 17 β -estradiol has a solubility in the solubilizing agent of at least about 12 mg/g.

3. The pharmaceutical composition of claim 1, wherein at least about 14% by weight of the progesterone is solubilized in the solubilizing agent.

4. The pharmaceutical composition of claim 1, wherein the 17 β -estradiol is fully solubilized in the solubilizing agent.

5. The pharmaceutical composition of claim 1, wherein the micronized progesterone has an X50 particle size value below about 15 microns, an X90 particle size value below about 25 microns, or both.

6. The pharmaceutical composition of claim 1, wherein the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides is about 1% to about 2% by weight of the fill material.

7. The pharmaceutical composition of claim 1, wherein the progesterone is about 33% by weight of the fill material.

8. The pharmaceutical composition of claim 1, wherein the mono- and diglycerides of capric and caprylic acid are about 65% by weight of the fill material.

9. The pharmaceutical composition of claim 1, wherein the 17 β -estradiol does not precipitate for at least about 14 days.

10. The pharmaceutical composition of claim 1, wherein the fill material has a total weight of less than about 400 mg.

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11. A pharmaceutical composition comprising: a fill material encapsulated in a soft gelatin capsule, the fill material comprising:

- a. two active pharmaceutical ingredients, the active pharmaceutical ingredients being about 1 mg of 17 β -estradiol and about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized, a second portion of the progesterone is micronized, and the 17 β -estradiol is fully solubilized; 5
- b. a solubilizing agent for the active pharmaceutical ingredients, the solubilizing agent comprising:
 - i. a medium chain oil comprising mono- and diglycerides; and
 - ii. at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides;

wherein the 17 β -estradiol and the progesterone in the capsule are present in the solubilizing agent; wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; and wherein the progesterone has a solubility in the solubilizing agent of at least about 73 mg/g and the 17 β -estradiol has a solubility in the solubilizing agent of at least about 10 mg/g.

12. The pharmaceutical composition of claim **11**, wherein the medium chain oil comprises mono- and diglycerides of capric and caprylic acid. 25

13. The pharmaceutical composition of claim **11**, wherein at least about 14% by weight of the progesterone is solubilized in the solubilizing agent. 30

14. The pharmaceutical composition of claim **11**, wherein the 17 β -estradiol has a solubility in the solubilizing agent of at least about 12 mg/g. 35

15. The pharmaceutical composition of claim **11**, wherein the micronized progesterone has an X50 particle size value below about 15 microns, an X90 particle size value below about 25 microns, or both. 40

16. The pharmaceutical composition of claim **11**, wherein the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides is about 1% to about 2% by weight of the fill material. 45

17. The pharmaceutical composition of claim **11**, wherein the progesterone is about 33% by weight of the fill material. 50

18. The pharmaceutical composition of claim **11**, wherein the medium chain oil is about 65% by weight of the fill material. 55

19. The pharmaceutical composition of claim **11**, wherein the 17 β -estradiol does not precipitate for at least about 14 days. 60

20. The pharmaceutical composition of claim **11**, wherein the fill material has a total weight of less than about 400 mg. 50

21. A pharmaceutical composition comprising: a fill material encapsulated in a capsule, the fill material comprising:

- a. two active pharmaceutical ingredients, the active pharmaceutical ingredients being about 1 mg of 17 β -estradiol and about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized, a second portion of the progesterone is micronized, and the 17 β -estradiol is fully solubilized; 55
- b. a solubilizing agent for the active pharmaceutical ingredients, the solubilizing agent comprising:
 - i. a medium chain oil comprising mono- and diglycerides of capric and caprylic acid that are about 65% by weight of the fill material; and

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ii. at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides that is about 1% to about 2% by weight of the fill material;

wherein the 17 β -estradiol and the progesterone in the capsule are present in the solubilizing agent; wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the progesterone has a solubility in the solubilizing agent of at least about 73 mg/g and the 17 β -estradiol has a solubility in the solubilizing agent of at least about 10 mg/g, wherein the 17 β -estradiol does not precipitate for at least about 14 days, and wherein the progesterone is about 33% by weight of the fill material.

22. The pharmaceutical composition of claim **21**, wherein at least about 14% by weight of the progesterone is solubilized in the solubilizing agent. 15

23. The pharmaceutical composition of claim **21**, wherein the 17 β -estradiol has a solubility in the solubilizing agent of at least about 12 mg/g. 20

24. The pharmaceutical composition of claim **21**, wherein the micronized progesterone has an X50 particle size value below about 15 microns, an X90 particle size value below about 25 microns, or both. 25

25. The pharmaceutical composition of claim **21**, wherein the fill material has a total weight of less than about 400 mg. 30

26. A pharmaceutical composition comprising: a fill material encapsulated in a capsule, the fill material comprising:

- a. two active pharmaceutical ingredients, the active pharmaceutical ingredients being about 1 mg of 17 β -estradiol and about 100 mg of progesterone, wherein at least about 90% of the 17 β -estradiol is solubilized, and wherein a first portion of the progesterone is solubilized and a second portion of the progesterone is micronized;
- b. a solubilizing agent for the active pharmaceutical ingredients;

wherein the 17 β -estradiol and the progesterone in the capsule are present in the solubilizing agent; wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; and wherein the progesterone has a solubility in the solubilizing agent of at least about 73 mg/g, and the 17 β -estradiol has a solubility in the solubilizing agent of at least about 10 mg/g.

27. The pharmaceutical composition of claim **26**, wherein the solubilizing agent comprises (i) monoglycerides and diglycerides of caprylic and capric acid; and (ii) at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides; wherein the mono- and diglycerides of capric and caprylic acid are about 65% by weight of the fill material, and the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides is about 1% by weight of the fill material. 45

28. The pharmaceutical composition of claim **1**, wherein up to about 14% by weight of the progesterone is solubilized in the solubilizing agent. 55

29. The pharmaceutical composition of claim **11**, wherein up to about 14% by weight of the progesterone is solubilized in the solubilizing agent. 60

30. The pharmaceutical composition of claim **21**, wherein up to about 14% by weight of the progesterone is solubilized in the solubilizing agent. 65

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EXHIBIT R



US011110099B2

(12) **United States Patent**
Bernick et al.

(10) **Patent No.:** US 11,110,099 B2
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(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(58) **Field of Classification Search**

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(56)

References Cited

U.S. PATENT DOCUMENTS

1,967,351 A	1/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	6/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopflin et al.

(Continued)

FOREIGN PATENT DOCUMENTS

BR	PI1001367-9 A2	7/2012
CA	2044371 A1	12/1991

(Continued)

OTHER PUBLICATIONS

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)
Activella® (estradiol/ norethindrone acetate) prescribing information (Nov. 2017) FDA Label, 39 pages.
Castelo-Branco, C., and Rostro, F., "Treatment of atrophic vaginitis," *Therapy*, 4(3): 349-353, Future Medicine Ltd., London, England (2007).

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

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(56)

References Cited

U.S. PATENT DOCUMENTS

4,014,334 A	3/1977	Theeuwes et al.	5,607,691 A	3/1997	Hale et al.
4,014,987 A	3/1977	Heller et al.	5,607,693 A	3/1997	Bonte et al.
4,016,251 A	8/1977	Higuchi et al.	5,609,617 A	3/1997	Shealy et al.
4,071,623 A	1/1978	van der Vies	5,620,705 A	4/1997	Dong et al.
4,093,709 A	6/1978	Choi et al.	5,626,866 A	5/1997	Ebert et al.
4,154,820 A	5/1979	Simoons	5,629,021 A	5/1997	Wright
4,155,991 A	5/1979	Schopflin et al.	5,633,011 A	5/1997	Dong et al.
4,196,188 A	4/1980	Besins	5,633,242 A	5/1997	Oettel et al.
4,215,691 A	8/1980	Wong	5,639,743 A	6/1997	Kaswan et al.
4,237,885 A	12/1980	Wong et al.	5,645,856 A	7/1997	Lacy et al.
4,310,510 A	1/1982	Sherman et al.	5,653,983 A	8/1997	Meybeck et al.
4,327,725 A	5/1982	Cortese et al.	5,656,286 A	8/1997	Miranda et al.
4,372,951 A	2/1983	Vorys	5,660,839 A	8/1997	Allec et al.
4,384,096 A	5/1983	Sonnabend	5,662,927 A	9/1997	Ehrlich et al.
4,393,871 A	7/1983	Vorhauer et al.	5,663,160 A	9/1997	Meybeck et al.
4,402,695 A	9/1983	Wong	5,676,968 A	10/1997	Lipp et al.
4,423,151 A	12/1983	Baranezuk	5,677,292 A	10/1997	Li et al.
4,449,980 A	5/1984	Millar et al.	5,686,097 A	11/1997	Taskovich et al.
4,610,687 A	9/1986	Fogwell	5,693,335 A	12/1997	Xia et al.
4,629,449 A	12/1986	Wong	5,694,947 A	12/1997	Lehtinen et al.
4,732,763 A	3/1988	Beck et al.	5,700,480 A	12/1997	Hille et al.
4,738,957 A	4/1988	Laurent et al.	5,709,844 A	1/1998	Arbeit et al.
4,756,907 A	7/1988	Beck et al.	5,719,197 A	2/1998	Kanios et al.
4,762,717 A	8/1988	Crowley, Jr.	5,735,801 A	4/1998	Caillouette
4,788,062 A	11/1988	Gale et al.	5,739,176 A	4/1998	Dunn et al.
4,816,257 A	3/1989	Buster et al.	5,744,463 A	4/1998	Bair
4,822,616 A	4/1989	Zimmermann et al.	5,747,058 A	5/1998	Tipton et al.
4,865,848 A	9/1989	Cheng et al.	5,762,614 A	6/1998	Caillouette
4,900,734 A	2/1990	Maxson et al.	5,770,176 A	6/1998	Nargessi
4,906,475 A	3/1990	Kim	5,770,219 A	6/1998	Chiang et al.
4,942,158 A	7/1990	Sarpotdar et al.	5,770,220 A	6/1998	Meconi et al.
4,961,931 A	10/1990	Wong	5,770,227 A	6/1998	Dong et al.
5,030,629 A	7/1991	Rajadhyaksha	5,776,495 A	7/1998	Duclos et al.
5,043,331 A	8/1991	Hirvonen et al.	5,780,044 A	7/1998	Yewey et al.
5,059,426 A	10/1991	Chiang et al.	5,780,050 A	7/1998	Jain et al.
5,064,654 A	11/1991	Berner et al.	5,788,980 A	8/1998	Nabahi
5,108,995 A	4/1992	Casper	5,788,984 A	8/1998	Guenther et al.
5,128,138 A	7/1992	Blank	5,789,442 A	8/1998	Garfield et al.
5,130,137 A	7/1992	Crowley, Jr.	5,811,416 A	9/1998	Chwalisz et al.
5,140,021 A	8/1992	Maxson et al.	5,811,547 A	9/1998	Nakamichi et al.
5,145,682 A	9/1992	Chien et al.	5,814,329 A	9/1998	Shah
5,208,225 A	5/1993	Boissonault et al.	5,820,878 A	10/1998	Hirano et al.
5,211,952 A	5/1993	Spicer et al.	5,827,200 A	10/1998	Caillouette
5,252,334 A	10/1993	Chiang et al.	5,840,327 A	11/1998	Gale et al.
5,280,023 A	1/1994	Ehrlich et al.	5,843,468 A	12/1998	Burkoth et al.
5,288,496 A	2/1994	Lewis	5,843,979 A	12/1998	Wille et al.
5,340,584 A	8/1994	Spicer et al.	5,858,394 A	1/1999	Lipp et al.
5,340,585 A	8/1994	Pike et al.	5,863,552 A	1/1999	Yue
5,340,586 A	8/1994	Pike et al.	5,866,603 A	2/1999	Li et al.
5,362,497 A	8/1994	Yamada et al.	5,869,084 A	2/1999	Paradissis et al.
5,382,573 A	1/1995	Casper	5,882,676 A	3/1999	Lee et al.
5,393,528 A	2/1995	Staab	5,885,612 A	3/1999	Meconi et al.
5,393,529 A	2/1995	Hoffmann et al.	5,888,533 A	3/1999	Dunn
5,419,910 A	5/1995	Lewis	5,891,462 A	4/1999	Carrara
5,453,279 A	9/1995	Lee et al.	5,891,868 A	4/1999	Cummings et al.
5,468,736 A	11/1995	Hodgen	5,898,038 A	4/1999	Yallampalli et al.
5,474,783 A	12/1995	Miranda et al.	5,902,603 A	5/1999	Chen et al.
5,480,776 A	1/1996	Dullien	5,904,931 A	5/1999	Lipp et al.
5,514,673 A	5/1996	Heckenmueller et al.	5,906,830 A	5/1999	Farinas et al.
5,516,528 A	5/1996	Hughes et al.	5,912,010 A	6/1999	Wille et al.
5,527,534 A	6/1996	Myhling	5,916,176 A	6/1999	Caillouette
5,529,782 A	6/1996	Staab	RE36,247 E	7/1999	Plunkett et al.
5,538,736 A	7/1996	Hoffmann et al.	5,919,477 A	7/1999	Bevan et al.
5,543,150 A	8/1996	Bologna et al.	5,922,349 A	7/1999	Elliesen et al.
5,547,948 A	8/1996	Barcomb	5,928,666 A	7/1999	Farinas et al.
5,556,635 A	9/1996	Istin et al.	5,942,243 A	8/1999	Shah
5,565,199 A	10/1996	Page et al.	5,942,531 A	8/1999	Diaz et al.
5,567,831 A	10/1996	Li	5,952,000 A	9/1999	Venkateshwaran et al.
5,569,652 A	10/1996	Beier et al.	5,958,446 A	9/1999	Miranda et al.
5,580,572 A	12/1996	Mikler et al.	5,962,445 A	10/1999	Stewart
5,582,592 A	12/1996	Kendrick	5,968,919 A	10/1999	Samour et al.
5,585,370 A	12/1996	Casper	5,972,372 A	10/1999	Saleh et al.
5,595,759 A	1/1997	Wright et al.	5,985,311 A	11/1999	Cordes et al.
5,595,970 A	1/1997	Garfield et al.	5,985,850 A	11/1999	Falk et al.
5,605,702 A	2/1997	Teillaud et al.	5,985,861 A	11/1999	Levine et al.
			5,993,856 A	11/1999	Ragavan et al.
			5,989,568 A	12/1999	Breton et al.
			6,001,846 A	12/1999	Edwards et al.
			6,007,835 A	12/1999	Bon Lapillonne et al.

US 11,110,099 B2

Page 3

(56)

References Cited**U.S. PATENT DOCUMENTS**

6,010,715 A	1/2000	Wick et al.	6,432,438 B1	8/2002	Shukla
6,013,276 A	1/2000	Math et al.	6,436,633 B1	8/2002	Kreider et al.
6,022,562 A	2/2000	Autant et al.	6,440,454 B1	8/2002	Santoro et al.
6,024,974 A	2/2000	Li	6,444,224 B1	9/2002	Rathbone et al.
6,024,976 A	2/2000	Miranda et al.	6,444,234 B1	9/2002	Kirby et al.
6,028,057 A	2/2000	Burns	6,451,300 B1	9/2002	Dunlop et al.
6,030,948 A	2/2000	Mann	6,451,339 B2	9/2002	Patel et al.
6,039,968 A	3/2000	Nabahi	6,451,779 B1	9/2002	Hesch
6,040,340 A	3/2000	Chwalisz et al.	6,455,246 B1	9/2002	Howett et al.
6,056,972 A	5/2000	Hermsmeyer	6,465,006 B1	10/2002	Zhang et al.
6,060,077 A	5/2000	Meignant	6,468,526 B2	10/2002	Chrisope
6,068,853 A	5/2000	Giannos et al.	6,469,016 B1	10/2002	Place et al.
6,074,625 A	6/2000	Hawthorne et al.	6,472,434 B1	10/2002	Place et al.
6,077,531 A	6/2000	Salin-Drouin	6,479,232 B1	11/2002	Howett et al.
6,080,118 A	6/2000	Blythe	6,495,160 B2	12/2002	Esposito et al.
6,083,178 A	7/2000	Caillouette	6,500,814 B1	12/2002	Hesch
6,086,916 A	7/2000	Agnus et al.	6,503,896 B1	1/2003	Tanabe et al.
6,087,352 A	7/2000	Trout	6,511,969 B1	1/2003	Hermsmeyer
6,090,404 A	7/2000	Meconi et al.	6,521,250 B2	2/2003	Meconi et al.
6,096,338 A	7/2000	Lacy et al.	6,526,980 B1	3/2003	Tracy et al.
6,106,848 A	8/2000	Preuilh et al.	6,528,094 B1	3/2003	Savoir et al.
6,117,446 A	9/2000	Place	6,531,149 B1	3/2003	Kirstgen et al.
6,117,450 A	9/2000	Dittgen et al.	6,537,580 B1	3/2003	Savoir et al.
6,124,362 A	9/2000	Bradbury et al.	6,538,039 B2	3/2003	Laurent
6,133,251 A	10/2000	Dittgen et al.	6,544,196 B2	4/2003	Caillouette
6,133,320 A	10/2000	Yallampalli et al.	6,544,553 B1	4/2003	Hsia et al.
6,139,868 A	10/2000	Hoffmann	6,548,053 B1	4/2003	Stewart et al.
6,139,873 A	10/2000	Hughes, Jr. et al.	6,548,491 B2	4/2003	Tanabe et al.
6,149,935 A	11/2000	Chiang et al.	6,551,611 B2	4/2003	Elliesen et al.
6,153,216 A	11/2000	Cordes et al.	6,555,131 B1	4/2003	Wolff et al.
6,165,491 A	12/2000	Grasset et al.	6,562,367 B1	5/2003	Wolff et al.
6,165,975 A	12/2000	Adams et al.	6,562,370 B2	5/2003	Luo et al.
6,187,323 B1	2/2001	Aiache et al.	6,562,790 B2	5/2003	Chein
6,187,339 B1	2/2001	de Haan et al.	6,569,463 B2	5/2003	Patel et al.
6,190,331 B1	2/2001	Caillouette	6,583,129 B1	6/2003	Mazer et al.
6,201,072 B1	3/2001	Rathi et al.	6,586,006 B2	7/2003	Roser et al.
6,217,886 B1	4/2001	Onyuksel et al.	6,589,549 B2	7/2003	Shih et al.
6,225,297 B1	5/2001	Stockemann et al.	6,593,317 B1	7/2003	de Ziegler et al.
6,227,202 B1	5/2001	Matapurkar	6,599,519 B1	7/2003	Seo et al.
6,228,383 B1	5/2001	Hansen et al.	6,610,325 B1	8/2003	Meignant et al.
6,228,852 B1	5/2001	Shaak	6,610,652 B2	8/2003	Adams et al.
6,242,509 B1	6/2001	Berger et al.	6,610,670 B2	8/2003	Blickensfeld et al.
6,245,811 B1	6/2001	Horrobin et al.	6,610,674 B1	8/2003	Schreiber
6,262,115 B1	7/2001	Guitard et al.	6,635,274 B1	10/2003	Masiz et al.
6,267,984 B1	7/2001	Beste et al.	6,638,528 B1	10/2003	Kanios
6,274,165 B1	8/2001	Meconi et al.	6,638,536 B2	10/2003	Savoir et al.
6,277,418 B1	8/2001	Marakverich et al.	6,645,528 B1	11/2003	Straub et al.
6,283,927 B1	9/2001	Caillouette	6,649,155 B1	11/2003	Dunlop et al.
6,284,263 B1	9/2001	Place	6,653,298 B2	11/2003	Potter et al.
6,287,588 B1	9/2001	Shih et al.	6,656,929 B1	12/2003	Agnus et al.
6,287,693 B1	9/2001	Savoir et al.	6,660,726 B2	12/2003	Hill et al.
6,291,527 B1	9/2001	Giorgetti	6,663,608 B2	12/2003	Rathbone et al.
6,294,188 B1	9/2001	Ragavan et al.	6,663,895 B2	12/2003	Savoir et al.
6,294,192 B1	9/2001	Patel et al.	6,664,296 B1	12/2003	Meignant
6,294,550 B1	9/2001	Place et al.	6,682,757 B1	1/2004	Wright
6,299,900 B1	10/2001	Reed et al.	6,692,763 B1	2/2004	Cummings et al.
6,303,132 B1	10/2001	Nelson	6,708,822 B1	3/2004	Muni
6,303,588 B1	10/2001	Danielov	6,716,454 B2	4/2004	Meignant et al.
6,306,841 B1	10/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.
6,306,914 B1	10/2001	de Ziegler et al.	6,737,081 B2	5/2004	Savoir et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,740,333 B2	5/2004	Beckett et al.
6,309,848 B1	10/2001	Howett et al.	6,743,448 B2	6/2004	Kryger
6,312,703 B1	11/2001	Orthoefer	6,748,815 B2	6/2004	Huebner et al.
6,328,987 B1	12/2001	Marini	6,747,018 B2	6/2004	Tanabe et al.
6,342,491 B1	1/2002	Dey et al.	6,750,291 B2	6/2004	Kim et al.
6,344,211 B1	2/2002	Hille	6,756,208 B2	6/2004	Griffin et al.
6,372,209 B1	4/2002	Chrisope	6,776,164 B2	8/2004	Bunt et al.
6,372,245 B1	4/2002	Bowman et al.	6,787,152 B2	9/2004	Kirby et al.
6,372,246 B1	4/2002	Wei et al.	6,805,877 B2	10/2004	Massara et al.
6,387,390 B1	5/2002	Deaver et al.	6,809,085 B1	10/2004	Elson et al.
6,402,705 B1	6/2002	Caillouette	6,818,226 B2	11/2004	Reed et al.
6,416,778 B1	7/2002	Ragavan et al.	6,821,524 B2	11/2004	Marini
6,420,352 B1	7/2002	Knowles	6,841,716 B1	1/2005	Tsutsumi
6,423,039 B1	7/2002	Rathbone et al.	6,844,334 B2	1/2005	Hill et al.
6,423,683 B1	7/2002	Heaton et al.	6,855,703 B1	2/2005	Hill et al.
			6,860,859 B2	3/2005	Mehrotra et al.

US 11,110,099 B2

Page 4

(56)	References Cited					
U.S. PATENT DOCUMENTS						
6,866,865 B2	3/2005	Hsia et al.	7,569,274 B2	8/2009	Besse et al.	
6,869,969 B2	3/2005	Huebner et al.	7,572,779 B2	8/2009	AloBl et al.	
6,878,518 B2	4/2005	Whitehead	7,572,780 B2	8/2009	Hermsmeyer	
6,901,278 B1	5/2005	Notelovitz	7,589,082 B2	9/2009	Savoir et al.	
6,905,705 B2	6/2005	Palm et al.	7,671,027 B2	3/2010	Loumaye	
6,911,211 B2	6/2005	Eini et al.	7,674,783 B2	3/2010	Hermsmeyer	
6,911,438 B2	6/2005	Wright	7,687,281 B2	3/2010	Roth et al.	
6,923,988 B2	8/2005	Patel et al.	7,687,485 B2	3/2010	Levinson et al.	
6,924,274 B2	8/2005	Lardy et al.	7,694,683 B2	4/2010	Callister et al.	
6,932,983 B1	8/2005	Straub et al.	7,704,983 B1	4/2010	Hodgen et al.	
6,939,558 B2	9/2005	Massara et al.	7,727,720 B2	6/2010	Dhallan	
6,943,021 B2	9/2005	Klausner et al.	7,732,408 B2	6/2010	Josephson et al.	
6,958,327 B1	10/2005	Hillisch et al.	7,749,989 B2	7/2010	Hill et al.	
6,960,337 B2	11/2005	Daniels et al.	7,767,656 B2	8/2010	Shoichet et al.	
6,962,691 B1	11/2005	Lulla et al.	7,799,769 B2	9/2010	White et al.	
6,962,908 B2	11/2005	AloBl et al.	7,815,936 B2	10/2010	Hasenzahl et al.	
6,967,194 B1	11/2005	Matsuo et al.	7,815,949 B2	10/2010	Cohen	
6,974,569 B2	12/2005	Dunlop et al.	7,829,115 B2	11/2010	Besins et al.	
6,977,250 B2	12/2005	Rodriguez	7,829,116 B2	11/2010	Griswold et al.	
6,978,945 B2	12/2005	Wong et al.	RE42,012 E	12/2010	Deaver et al.	
6,987,129 B2	1/2006	Mak et al.	7,850,992 B2	12/2010	Kim et al.	
6,995,149 B1	2/2006	Endrikat et al.	7,854,753 B2	12/2010	Kraft et al.	
7,004,321 B1	2/2006	Palm et al.	7,858,607 B2	12/2010	Mamchur	
7,005,429 B2	2/2006	Dey et al.	RE42,072 E	1/2011	Deaver et al.	
7,011,846 B2	3/2006	Shojaei et al.	7,884,093 B2	2/2011	Creasy et al.	
7,018,992 B2	3/2006	Koch et al.	7,925,519 B2	4/2011	Greene	
7,030,104 B2	4/2006	Gray et al.	7,939,104 B2	5/2011	Blrbera et al.	
7,030,157 B2	4/2006	Ke et al.	7,943,602 B2	5/2011	Bunschoten et al.	
RE39,104 E	5/2006	Duclos et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.	
7,074,779 B2	7/2006	Sui et al.	7,945,459 B2	5/2011	Grace et al.	
7,083,590 B1	8/2006	Bunt et al.	7,960,368 B2	6/2011	Nickisch et al.	
7,091,213 B2	8/2006	Metcalf, III et al.	7,989,436 B2	8/2011	Hill et al.	
7,094,228 B2	8/2006	Zhang et al.	7,989,487 B2	8/2011	Welsh et al.	
7,097,853 B1	8/2006	Garbe et al.	8,022,053 B2	9/2011	Mueller et al.	
7,101,342 B1	9/2006	Caillouette	8,048,017 B2	11/2011	Xu	
7,105,573 B2	9/2006	Krajcik et al.	8,048,869 B2	11/2011	Bunschoten et al.	
7,135,190 B2	11/2006	Piao et al.	8,063,030 B2	11/2011	Ellman	
7,153,522 B1	12/2006	Ikeura et al.	8,071,576 B2	12/2011	Coelingh Bennink et al.	
7,163,681 B2	1/2007	Giles-Komar et al.	8,071,729 B2	12/2011	Giles-Komar et al.	
7,163,699 B2	1/2007	Besse	8,075,916 B2	12/2011	Song et al.	
7,175,850 B2	2/2007	Cevc	8,075,917 B2	12/2011	Chung et al.	
7,179,799 B2	2/2007	Hill et al.	8,076,317 B2	12/2011	Kulmann	
7,196,074 B2	3/2007	Blye et al.	8,076,319 B2	12/2011	Leonard	
7,198,800 B1	4/2007	Ko	8,080,553 B2	12/2011	Keith et al.	
7,198,801 B2	4/2007	Carrara et al.	8,088,605 B2	1/2012	Beudet et al.	
7,226,910 B2	6/2007	Wilson et al.	8,096,940 B2	1/2012	Josephson et al.	
7,247,625 B2	7/2007	Zhang et al.	8,101,209 B2	1/2012	Legrand et al.	
7,250,446 B2	7/2007	Sangita et al.	8,101,773 B2	1/2012	Smith et al.	
7,267,829 B2	9/2007	Kirby et al.	8,114,152 B2	2/2012	Furst	
7,300,926 B2	11/2007	Prokai et al.	8,114,434 B2	2/2012	Sasaki et al.	
7,303,763 B2	12/2007	Ho	8,114,442 B2	2/2012	Tucker et al.	
7,317,037 B2	1/2008	Fensome et al.	8,119,741 B2	2/2012	Pavlin	
7,329,654 B2	2/2008	Kanojia et al.	8,121,886 B2	2/2012	Azar	
7,335,650 B2	2/2008	Potter et al.	8,124,118 B2	2/2012	Lennernaes et al.	
7,374,779 B2	5/2008	Chen et al.	8,124,595 B2	2/2012	Boissonneault	
7,378,404 B2	5/2008	Peters et al.	8,147,561 B2	4/2012	Binmoeller	
7,381,427 B2	6/2008	Ancira et al.	8,148,546 B2	4/2012	Schuster et al.	
7,387,789 B2	6/2008	Klose et al.	8,158,613 B2	4/2012	Staniforth et al.	
7,388,006 B2	6/2008	Schmees et al.	8,158,614 B2	4/2012	Lambert et al.	
7,414,043 B2	8/2008	Kosemund et al.	8,163,722 B2	4/2012	Savoir et al.	
7,427,413 B2	9/2008	Savoir et al.	8,177,449 B2	5/2012	Watkinson et al.	
7,427,609 B2	9/2008	Leonard	8,182,833 B2	5/2012	Hermsmeyer	
7,429,576 B2	9/2008	Labrie	8,187,615 B2	5/2012	Friedman	
7,431,941 B2	10/2008	Besins et al.	8,187,640 B2	5/2012	Dunn	
7,456,159 B2	11/2008	Houze et al.	8,195,403 B2	6/2012	Ishikawa et al.	
7,459,445 B2	12/2008	Hill et al.	8,202,736 B2	6/2012	Mousa et al.	
7,465,587 B2	12/2008	Imrich	8,217,024 B2	7/2012	Ahmed et al.	
7,470,433 B2	12/2008	Carrara et al.	8,221,785 B2	7/2012	Chien	
7,485,666 B2	2/2009	Villaneuva et al.	8,222,008 B2	7/2012	Thoene	
7,497,855 B2	3/2009	Ausiello et al.	8,222,237 B2	7/2012	Nickisch et al.	
7,498,303 B2	3/2009	Arnold et al.	8,227,454 B2	7/2012	Hill et al.	
7,534,765 B2	5/2009	Gregg et al.	8,227,509 B2	7/2012	Castro et al.	
7,534,780 B2	5/2009	Wyrwa et al.	8,241,664 B2	8/2012	Dudley et al.	
7,550,142 B2	6/2009	Giles-Komar et al.	8,247,393 B2	8/2012	Ahmed et al.	
7,563,565 B1	7/2009	Matsuo et al.	8,257,724 B2	9/2012	Cromack et al.	

US 11,110,099 B2

Page 5

(56)	References Cited					
U.S. PATENT DOCUMENTS						
8,257,725 B2	9/2012	Cromack et al.	8,784,882 B2	7/2014	Mattern	
8,268,352 B2	9/2012	Vaya et al.	8,846,648 B2	9/2014	Bernick et al.	
8,268,806 B2	9/2012	Labrie	8,846,649 B2	9/2014	Bernick et al.	
8,268,878 B2	9/2012	Armer et al.	8,993,549 B2	3/2015	Bernick et al.	
8,273,730 B2	9/2012	Fernandez et al.	9,006,222 B2	3/2015	Bernick et al.	
8,287,888 B2	10/2012	Song et al.	9,012,434 B2	4/2015	Bernick et al.	
8,288,366 B2	10/2012	Chochinov et al.	9,114,145 B2	8/2015	Bernick et al.	
8,318,898 B2	11/2012	Fasel et al.	9,114,146 B2	8/2015	Bernick et al.	
8,324,193 B2	12/2012	Lee Sepsick et al.	9,180,091 B2	11/2015	Bernick et al.	
8,329,680 B2	12/2012	Evans et al.	9,248,136 B2	2/2016	Bernick et al.	
8,337,814 B2	12/2012	Osbikken et al.	9,289,382 B2	3/2016	Bernick et al.	
8,344,007 B2	1/2013	Tang et al.	9,301,920 B2	4/2016	Bernick et al.	
8,349,820 B2	1/2013	Zeun et al.	9,931,349 B2	4/2018	Shadiack et al.	
8,353,863 B2	1/2013	Imran	10,052,386 B2	8/2018	Bernick et al.	
8,357,723 B2	1/2013	Satyam	10,098,894 B2	10/2018	Amadio et al.	
8,361,995 B2	1/2013	Schramm	10,206,932 B2	2/2019	Bernick et al.	
8,362,091 B2	1/2013	Tamarkin et al.	10,258,630 B2	4/2019	Mirkin et al.	
8,372,424 B2	2/2013	Berry et al.	10,398,708 B2	9/2019	Mirkin et al.	
8,372,806 B2	2/2013	Boehler et al.	10,471,072 B2	11/2019	Bernick et al.	
8,377,482 B2	2/2013	Laurie et al.	10,537,581 B2	1/2020	Bernick et al.	
8,377,994 B2	2/2013	Gray et al.	10,568,891 B2	2/2020	Mirkin et al.	
8,394,759 B2	3/2013	B1rathur et al.	10,668,082 B2	6/2020	Mirkin et al.	
8,415,332 B2	4/2013	Diliberti et al.	10,675,288 B2	6/2020	Bernick et al.	
8,420,111 B2	4/2013	Hermsmeyer	10,806,697 B2	10/2020	Bernick et al.	
8,435,561 B2	5/2013	Besins et al.	10,806,740 B2	10/2020	Persicaner et al.	
8,435,972 B2	5/2013	Stein et al.	10,835,487 B2	11/2020	Bernick et al.	
8,449,879 B2	5/2013	Laurent Applegate et al.	10,888,516 B2	1/2021	Bernick et al.	
8,450,108 B2	5/2013	Boyce	2001/0005728 A1	2/2001	Guittard et al.	
8,454,945 B2	6/2013	McCook et al.	2001/0009673 A1	7/2001	Lipp et al.	
8,455,468 B2	6/2013	Hoffman et al.	2001/0021816 A1	9/2001	Caillouette	
8,461,138 B2	6/2013	Boissonault	2001/0023261 A1	9/2001	Ryoo et al.	
8,476,252 B2	7/2013	Achleitner et al.	2001/0027189 A1	10/2001	Bennink et al.	
8,481,488 B2	7/2013	Carter	2001/0029357 A1	10/2001	Bunt et al.	
8,486,374 B2	7/2013	Tamarkin et al.	2001/0031747 A1	10/2001	de Ziegler et al.	
8,486,442 B2	7/2013	Matsushita et al.	2001/0032125 A1	10/2001	Bhan et al.	
8,492,368 B2	7/2013	Vanlandingham et al.	2001/0034340 A1	10/2001	Pickar	
8,507,467 B2	8/2013	Matsui et al.	2012/0269878 A2	10/2001	Cantor et al.	
8,512,693 B2	8/2013	Capito et al.	2001/0053383 A1	12/2001	Miranda et al.	
8,512,754 B2	8/2013	Needham	2001/0056068 A1	12/2001	Chwalisz et al.	
8,518,376 B2	8/2013	Tamarkin et al.	2002/0012710 A1	1/2002	Lansky	
8,536,159 B2	9/2013	Li et al.	2002/0026158 A1	2/2002	Rathbone et al.	
8,540,967 B2	9/2013	Trivedi et al.	2002/0028788 A1	3/2002	Bunt et al.	
8,541,400 B2	9/2013	Johnsson et al.	2002/0035070 A1	3/2002	Gardlik et al.	
8,551,462 B2	10/2013	Goldstein et al.	2002/0058648 A1	5/2002	Hammerly	
8,557,281 B2	10/2013	Halliday et al.	2002/0058926 A1	5/2002	Rathbone et al.	
8,568,374 B2	10/2013	De Graaff et al.	2002/0064541 A1	5/2002	Lapidot et al.	
8,591,951 B2	11/2013	Kohn et al.	2002/0076441 A1	6/2002	Shih et al.	
8,613,951 B2	12/2013	Zale et al.	2002/0102308 A1	8/2002	Wei et al.	
8,633,178 B2	1/2014	Bernick et al.	2002/0107230 A1	8/2002	Waldon et al.	
8,633,180 B2	1/2014	Li et al.	2002/0114803 A1	8/2002	Deaver et al.	
8,636,787 B2	1/2014	Sabiria	2002/0119174 A1	8/2002	Gardlik et al.	
8,636,982 B2	1/2014	Tamarkin et al.	2002/0119198 A1	8/2002	Gao et al.	
8,653,129 B2	2/2014	Fein et al.	2002/0132801 A1	9/2002	Heil et al.	
8,658,627 B2	2/2014	Voskuhl	2002/0137749 A1	9/2002	Levinson et al.	
8,658,628 B2	2/2014	Blucom	2002/0142017 A1	10/2002	Simonnet	
8,663,681 B2	3/2014	Ahmed et al.	2002/0151530 A1	10/2002	Leonard et al.	
8,663,692 B2	3/2014	Mueller et al.	2002/0156394 A1	10/2002	Mehrotra et al.	
8,663,703 B2	3/2014	Lerner et al.	2002/0169150 A1	11/2002	Pickar	
8,664,207 B2	3/2014	Li et al.	2002/0169205 A1	11/2002	Chwalisz et al.	
8,669,293 B2	3/2014	Levy et al.	2002/0173510 A1	11/2002	Levinson et al.	
8,679,552 B2	3/2014	Guthery	2002/0193356 A1	12/2002	Van Beek et al.	
8,694,358 B2	4/2014	Tryfon	2002/0193758 A1	12/2002	Sandberg	
8,697,127 B2	4/2014	Sah	2002/0197286 A1	12/2002	Brandman et al.	
8,697,710 B2	4/2014	Li et al.	2003/0003139 A1	1/2003	Lipp et al.	
8,703,105 B2	4/2014	Tamarkin et al.	2003/0004145 A1	1/2003	Leonard	
8,709,385 B2	4/2014	Tamarkin et al.	2003/0007994 A1	1/2003	Bunt et al.	
8,709,451 B2	4/2014	Nam et al.	2003/0027772 A1	2/2003	Breton	
8,715,735 B2	5/2014	Funke et al.	2003/0091620 A1	2/2003	Fikstad et al.	
8,721,331 B2	5/2014	Raghuprasad	2003/0044453 A1	3/2003	Dittgen et al.	
8,722,021 B2	5/2014	Friedman et al.	2003/0049307 A1	3/2003	Gyurik	
8,734,846 B2	5/2014	Ali et al.	2003/0064097 A1	4/2003	Patel et al.	
8,735,381 B2	5/2014	Podolski	2003/0064975 A1	4/2003	Koch et al.	
8,741,336 B2	6/2014	Dipierro et al.	2003/0072760 A1	4/2003	SirBlsku	
8,741,373 B2	6/2014	Bromley et al.	2003/0073248 A1	4/2003	Roth et al.	
8,753,661 B2	6/2014	Steinmueller Nethl et al.	2003/0073673 A1	4/2003	Hesch	

US 11,110,099 B2

Page 6

(56)

References Cited**U.S. PATENT DOCUMENTS**

2003/0077297 A1	4/2003	Chen et al.	2004/0225140 A1	11/2004	Fernandez et al.
2003/0078245 A1	4/2003	Bennink et al.	2004/0234606 A1	11/2004	Levine et al.
2003/0091640 A1	5/2003	Ramanathan et al.	2004/0241219 A1	12/2004	Hille et al.
2003/0092691 A1	5/2003	Besse et al.	2004/0243437 A1	12/2004	Grace et al.
2003/0096012 A1	5/2003	Besse et al.	2004/0253319 A1	12/2004	Netke et al.
2003/0104048 A1	6/2003	Patel et al.	2004/0259817 A1	12/2004	Waldon et al.
2003/0109507 A1	6/2003	Franke et al.	2004/0266745 A1	12/2004	Schwanitz et al.
2003/0113268 A1	6/2003	Buenafae et al.	2005/0003003 A1	1/2005	Deaver et al.
2003/0114420 A1	6/2003	Salvati et al.	2005/0004088 A1	1/2005	Hesch
2003/0114430 A1	6/2003	MacLeod et al.	2005/0009800 A1	1/2005	Thumbeck et al.
2003/0124182 A1	7/2003	Shojaei et al.	2005/0014729 A1	1/2005	Pulaski
2003/0124191 A1	7/2003	Besse et al.	2005/0020550 A1	1/2005	Morris et al.
2003/0130558 A1	7/2003	Massara et al.	2005/0020552 A1	1/2005	Aschkenasay et al.
2003/0144258 A1	7/2003	Heil et al.	2005/0021009 A1	1/2005	Massara et al.
2003/0157157 A1	8/2003	Luo et al.	2005/0025833 A1	2/2005	Aschkenasay et al.
2003/0166509 A1	9/2003	Bltycky et al.	2005/0031651 A1	2/2005	Gervais et al.
2003/0170295 A1	9/2003	Kim et al.	2005/0042173 A1	2/2005	Besse et al.
2003/0175329 A1	9/2003	Azarnoff et al.	2005/0042268 A1	2/2005	Aschkenasay et al.
2003/0175333 A1	9/2003	Shefer et al.	2005/0048116 A1	3/2005	Straub et al.
2003/0180352 A1	9/2003	Patel et al.	2005/0054991 A1	3/2005	Tobyn et al.
2003/0181353 A1	9/2003	Nyce	2005/0079138 A1	4/2005	Chickering, III et al.
2003/0181728 A1	9/2003	Salvati et al.	2005/0085453 A1	4/2005	Govindarajan
2003/0191096 A1	10/2003	Leonard et al.	2005/0101579 A1	5/2005	Shippen
2003/0195177 A1	10/2003	Leonard et al.	2005/0113350 A1	5/2005	Duesterberg et al.
2003/0215496 A1	11/2003	Patel et al.	2005/0118244 A1	6/2005	Theobld et al.
2003/0219402 A1	11/2003	Rutter	2005/0118272 A1	6/2005	Besse et al.
2003/0220297 A1	11/2003	Bernstein et al.	2005/0129756 A1	6/2005	Podhaisky et al.
2003/0224057 A1	12/2003	Martin-Letellier et al.	2005/0152956 A1	7/2005	Dudley
2003/0224059 A1	12/2003	Lerner et al.	2005/0153946 A1	7/2005	Hirsh et al.
2003/0225047 A1	12/2003	Caubel et al.	2005/0164977 A1	7/2005	Coelingh Bennink
2003/0225048 A1	12/2003	Caubel et al.	2005/0182105 A1	8/2005	Nirschl et al.
2003/0225050 A1	12/2003	Eichardt et al.	2005/0186141 A1	8/2005	Gonda et al.
2003/0228686 A1	12/2003	Klausner et al.	2005/0187267 A1	8/2005	Hamann et al.
2003/0229057 A1	12/2003	Caubel et al.	2005/0192253 A1	9/2005	Salvati et al.
2003/0235596 A1	12/2003	Gao et al.	2005/0192310 A1	9/2005	Gavai et al.
2003/0236236 A1	12/2003	Chen et al.	2005/0196434 A1	9/2005	Briere
2004/0009960 A1	1/2004	Heil et al.	2005/0207990 A1	9/2005	Funke et al.
2004/0022820 A1	2/2004	Anderson	2005/0209209 A1	9/2005	Koch et al.
2004/0034001 A1	2/2004	Karara	2005/0214384 A1	9/2005	Juturu et al.
2004/0037881 A1	2/2004	Guittard et al.	2005/0220825 A1	10/2005	Funke et al.
2004/0039356 A1	2/2004	Maki et al.	2005/0220900 A1	10/2005	Popp et al.
2004/0043043 A1	3/2004	Schlyter et al.	2005/0222106 A1	10/2005	Bracht
2004/0043943 A1	3/2004	Guittard et al.	2005/0228692 A1	10/2005	Hodgdon
2004/0044080 A1	3/2004	Place et al.	2005/0228718 A1	10/2005	Austin
2004/0048900 A1	3/2004	Flood	2005/0239747 A1	10/2005	Yang et al.
2004/0052824 A1	3/2004	Abou Chakra-Vernet et al.	2005/0239758 A1	10/2005	Roby
2004/0073024 A1	4/2004	Metcalf, III et al.	2005/0244360 A1	11/2005	Billoni
2004/0077605 A1	4/2004	Salvati et al.	2005/0244522 A1	11/2005	Carrara et al.
2004/0077606 A1	4/2004	Salvati et al.	2005/0245902 A1	11/2005	Cornish et al.
2004/0087548 A1	5/2004	Salvati et al.	2005/0250746 A1	11/2005	Iammatteo
2004/0087564 A1	5/2004	Wright et al.	2005/0250750 A1	11/2005	Cummings et al.
2004/0089308 A1	5/2004	Welch	2005/0250753 A1	11/2005	Fink et al.
2004/0092494 A9	5/2004	Dudley	2005/0256028 A1	11/2005	Yun et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0266078 A1	11/2005	Jorda et al.
2004/0093261 A1	5/2004	Jain et al.	2005/0266088 A1	12/2005	Hinrichs et al.
2004/0097468 A1	5/2004	Wimalawansa	2005/0271597 A1	12/2005	Keith
2004/0101557 A1	5/2004	Gibson et al.	2005/0271598 A1	12/2005	Friedman et al.
2004/0106542 A1	6/2004	Deaver et al.	2005/0272685 A1	12/2005	Hung
2004/0110732 A1	6/2004	Masini Eteve et al.	2005/0272712 A1	12/2005	GruB2 et al.
2004/0131670 A1	7/2004	Gao	2006/0009428 A1	1/2006	Grub2 et al.
2004/0138103 A1	7/2004	Patt	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0142012 A1	7/2004	Bunt et al.	2006/0018937 A1	1/2006	Friedman et al.
2004/0146539 A1	7/2004	Gupta	2006/0019978 A1	1/2006	Bilog
2004/0146894 A1	7/2004	Warrington et al.	2006/0020002 A1	1/2006	Salvati et al.
2004/0147578 A1	7/2004	Calvet	2006/0030615 A1	2/2006	Fensome et al.
2004/0161435 A1	8/2004	Gupta	2006/0034889 A1	2/2006	Jo et al.
2004/0176324 A1	9/2004	Salvati et al.	2006/0034904 A1	2/2006	Weimann
2004/0176336 A1	9/2004	Rodriguez	2006/0040904 A1	2/2006	Ahmed et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0052341 A1	3/2006	Cornish et al.
2004/0191276 A1	9/2004	Muni	2006/0069031 A1	3/2006	Loumaye
2004/0198706 A1	10/2004	Carrara et al.	2006/0078618 A1	4/2006	Constantinides et al.
2004/0210280 A1	10/2004	Liedtke	2006/0083778 A1	4/2006	Allison et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0100180 A1	4/2006	Shih et al.
2004/0219124 A1	11/2004	Gupta	2006/0106004 A1	4/2006	Meconi et al.
				5/2006	Casper et al.
				5/2006	Chickering, III et al.
				5/2006	Bohlmann et al.
				5/2006	Brody et al.

US 11,110,099 B2

Page 7

(56)	References Cited					
U.S. PATENT DOCUMENTS						
2006/0110415 A1	5/2006	Gupta	2007/0286819 A1	12/2007	DeVries et al.	
2006/0111424 A1	5/2006	Salvati et al.	2007/0287688 A1	12/2007	Chan et al.	
2006/0121102 A1	6/2006	Chiang	2007/0287789 A1	12/2007	Jones et al.	
2006/0121626 A1	6/2006	Imrich	2007/0292359 A1	12/2007	Friedman et al.	
2006/0134188 A1	6/2006	Podhaisky et al.	2007/0292387 A1	12/2007	Jon et al.	
2006/0135619 A1	6/2006	Kick et al.	2007/0292461 A1	12/2007	Tamarkin et al.	
2006/0165744 A1	7/2006	Jamil et al.	2007/0292493 A1	12/2007	Briere	
2006/0193789 A1	8/2006	Tamarkin et al.	2007/0298089 A1	12/2007	Saeki et al.	
2006/0194775 A1	8/2006	Tofovic et al.	2008/0026035 A1	1/2008	Chollet et al.	
2006/0204557 A1	9/2006	Gupta et al.	2008/0026040 A1	1/2008	Farr et al.	
2006/0233743 A1	10/2006	Kelly	2008/0026062 A1	1/2008	Farr et al.	
2006/0233841 A1	10/2006	Brodbeck et al.	2008/0038219 A1	2/2008	Carlson et al.	
2006/0235037 A1	10/2006	Purandare et al.	2008/0038350 A1	2/2008	Gerecke et al.	
2006/0240111 A1	10/2006	Fernandez et al.	2008/0039405 A1	2/2008	Langley et al.	
2006/0246122 A1	11/2006	Langguth et al.	2008/0050317 A1	2/2008	Tamarkin et al.	
2006/0247216 A1	11/2006	Haj-Yehia	2008/0051351 A1	2/2008	Ghisalberti	
2006/0247221 A1	11/2006	Coelingh Bennink et al.	2008/0063607 A1	3/2008	Tamarkin et al.	
2006/0251581 A1	11/2006	McIntyre et al.	2008/0069779 A1	3/2008	Tamarkin et al.	
2006/0252049 A1	11/2006	Shuler et al.	2008/0069791 A1	3/2008	Beissert	
2006/0257472 A1	11/2006	Neilsen	2008/0085877 A1	4/2008	Bortz	
2006/0275218 A1	12/2006	Tamarkin et al.	2008/0095831 A1	4/2008	McGraw	
2006/0275360 A1	12/2006	Ahmed et al.	2008/0095838 A1	4/2008	Abou Chacra-Vernet	
2006/0276414 A1	12/2006	Coelingh Bennink et al.	2008/0119537 A1	5/2008	Zhang et al.	
2006/0280771 A1	12/2006	Groenewegen et al.	2008/0125402 A1	5/2008	Dilberti	
2006/0280797 A1	12/2006	Shoichet et al.	2008/0138379 A1	6/2008	Jennings-Spring	
2006/0280800 A1	12/2006	Nagi et al.	2008/0138390 A1	6/2008	Hsu et al.	
2006/0292223 A1	12/2006	Woolfson et al.	2008/0139392 A1	6/2008	Acosta Zara et al.	
2007/0004693 A1	1/2007	Woolfson et al.	2008/0145423 A1	6/2008	Khan et al.	
2007/0004694 A1	1/2007	Woolfson et al.	2008/0153789 A1	6/2008	Dmowski et al.	
2007/0009559 A1	1/2007	Li et al.	2008/0175814 A1	7/2008	Phiasivongsa et al.	
2007/0009594 A1	1/2007	Grub2 et al.	2008/0175905 A1	7/2008	Liu et al.	
2007/0010550 A1	1/2007	McKenzie	2008/0175908 A1	7/2008	Liu et al.	
2007/0014839 A1	1/2007	Bracht	2008/0188829 A1	8/2008	Creasy	
2007/0015698 A1	1/2007	Kleinman et al.	2008/0206156 A1	8/2008	Cronk	
2007/0021360 A1	1/2007	Nyce et al.	2008/0206159 A1	8/2008	Tamarkin et al.	
2007/0027201 A1	2/2007	McComas et al.	2008/0206161 A1	8/2008	Tamarkin et al.	
2007/0031491 A1	2/2007	Levine et al.	2008/0214512 A1	9/2008	Seitz et al.	
2007/0036843 A1	2/2007	Hirsh et al.	2008/0220069 A1	9/2008	Allison	
2007/0037780 A1	2/2007	Ebert et al.	2008/0226698 A1	9/2008	Tang et al.	
2007/0037782 A1	2/2007	Hibino et al.	2008/0227763 A1	9/2008	Lanquetin et al.	
2007/0042038 A1	2/2007	Besse	2008/0234199 A1	9/2008	Katamreddy	
2007/0049567 A1	3/2007	Wiley	2008/0234240 A1	9/2008	Duesterberg et al.	
2007/0060589 A1	3/2007	Purandare et al.	2008/0255078 A1	10/2008	Katamreddy	
2007/0066628 A1	3/2007	Zhang et al.	2008/0255089 A1	10/2008	Katamreddy	
2007/0066637 A1	3/2007	Zhang et al.	2008/0261931 A1	10/2008	Hedner et al.	
2007/0066675 A1	3/2007	Zhang et al.	2008/0113953 A1	12/2008	DeVries et al.	
2007/0071777 A1	3/2007	Bromer et al.	2008/0114050 A1	12/2008	Fensome et al.	
2007/0078091 A1	4/2007	Hubler et al.	2008/0299220 A1	12/2008	Tamarkin et al.	
2007/0088029 A1	4/2007	Bllog et al.	2008/0306036 A1	12/2008	Katamreddy	
2007/0093548 A1	4/2007	Diffendal et al.	2008/0312197 A1	12/2008	Rodriguez	
2007/0116729 A1	5/2007	Palepu	2008/0312198 A1	12/2008	Rodriguez	
2007/0116829 A1	5/2007	Prakash et al.	2008/0319078 A1	12/2008	Katamreddy	
2007/0128263 A1	6/2007	Gargiulo et al.	2009/0004246 A1	1/2009	Woolfson et al.	
2007/0154533 A1	7/2007	Dudley	2009/0010968 A1	1/2009	Allart et al.	
2007/0167418 A1	7/2007	Ferguson	2009/0011041 A1	1/2009	Musaeva et al.	
2007/0178166 A1	8/2007	Bernstein et al.	2009/0017120 A1	1/2009	Trimble et al.	
2007/0184558 A1	8/2007	Roth et al.	2009/0022683 A1	1/2009	Song et al.	
2007/0185068 A1	8/2007	Ferguson et al.	2009/0047357 A1	2/2009	Tomohira et al.	
2007/0190022 A1	8/2007	Chiao et al.	2009/0053294 A1	2/2009	Prendergast	
2007/0191319 A1	8/2007	Ke et al.	2009/0060982 A1	3/2009	Ron et al.	
2007/0191321 A1	8/2007	Ahmed et al.	2009/0060997 A1	3/2009	Seitz et al.	
2007/0196415 A1	8/2007	Chen et al.	2009/0068118 A1	3/2009	Eini et al.	
2007/0196433 A1	8/2007	Ron et al.	2009/0074859 A1	3/2009	Patel	
2007/0207225 A1	9/2007	Squadrito	2009/0081206 A1	3/2009	Leibovitz	
2007/0225281 A1	9/2007	Zhang et al.	2009/0081278 A1	3/2009	De Graaff et al.	
2007/0232574 A1	10/2007	Galey et al.	2009/0081303 A1	3/2009	Savoir et al.	
2007/0238713 A1	10/2007	Gast et al.	2009/0092656 A1	4/2009	Klamerus et al.	
2007/0243229 A1	10/2007	Smith et al.	2009/0093440 A1	4/2009	Murad	
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0098069 A1	4/2009	Vacca	
2007/0254858 A1	11/2007	Cronk	2009/0099106 A1	4/2009	Phiasivongsa et al.	
2007/0255197 A1	11/2007	Humberstone et al.	2009/0099149 A1	4/2009	Liu et al.	
2007/0264309 A1	11/2007	Chollet et al.	2009/0130029 A1	5/2009	Tamarkin et al.	
2007/0264345 A1	11/2007	Eros et al.	2009/0131385 A1	5/2009	Voskuhl	
2007/0264349 A1	11/2007	Lee et al.	2009/0136574 A1	5/2009	Diaz-Astruc et al.	
2007/0270394 A1	11/2007	El-Alfy et al.	2009/0137538 A1	5/2009	Bernstein et al.	
			2009/014344 A1	6/2009	Klamerus et al.	
			2009/0164341 A1	6/2009	Chang	
			2009/0175799 A1	7/2009	Sunvold et al.	

US 11,110,099 B2

Page 8

(56)

References Cited**U.S. PATENT DOCUMENTS**

2009/0181088 A1	7/2009	Song et al.	2011/0142945 A1	6/2011	Chen et al.
2009/0186081 A1	7/2009	Holm et al.	2011/0152840 A1	6/2011	Lee et al.
2009/0197843 A1	8/2009	Notelovitz et al.	2011/0158920 A1	6/2011	Morley et al.
2009/0203658 A1	8/2009	Marx et al.	2011/0171140 A1	7/2011	Illum et al.
2009/0214474 A1	8/2009	Jennings	2011/0182997 A1	7/2011	Lewis et al.
2009/0227025 A1	9/2009	Nichols et al.	2011/0190201 A1	8/2011	Hyde et al.
2009/0227550 A1	9/2009	Mattern	2011/0195031 A1	8/2011	Du
2009/0232897 A1	9/2009	Sahoo et al.	2011/0195114 A1	8/2011	Carrara et al.
2009/0258096 A1	10/2009	Cohen	2011/0195944 A1	8/2011	Mura et al.
2009/0264395 A1	10/2009	Creasy	2011/0217341 A1	9/2011	Sah
2009/0269403 A1	10/2009	Shaked et al.	2011/0238003 A1	9/2011	Bruno Raimondi et al.
2009/0285772 A1	11/2009	Phasivongsa et al.	2011/0244043 A1	10/2011	Xu et al.
2009/0285869 A1	11/2009	Trimble	2011/0250256 A1	10/2011	Hyun Oh et al.
2009/0318558 A1	12/2009	Kim et al.	2011/0250259 A1	10/2011	Buckman
2009/0324714 A1	12/2009	Liu et al.	2011/0250274 A1	10/2011	Shaked et al.
2009/0325916 A1	12/2009	Zhang et al.	2011/0256092 A1	10/2011	Phasivongsa et al.
2010/0008985 A1	1/2010	Pellikaan et al.	2011/0262373 A1	10/2011	Umbert Millet
2010/0028360 A1	2/2010	Atwood	2011/0262494 A1	10/2011	Achleitner et al.
2010/0034838 A1	2/2010	Staniforth et al.	2011/0268665 A1	11/2011	Tamarkin et al.
2010/0034880 A1	2/2010	Sintov et al.	2011/0275584 A1	11/2011	Wilckens et al.
2010/0040671 A1	2/2010	Ahmed et al.	2011/0281832 A1	11/2011	Li et al.
2010/0048523 A1	2/2010	Blchman et al.	2011/0287094 A1	11/2011	Penhasi et al.
2010/0055138 A1	3/2010	Margulies et al.	2011/0293720 A1	12/2011	General et al.
2010/0074959 A1	3/2010	Hansom et al.	2011/0294738 A1	12/2011	Ren et al.
2010/0086501 A1	4/2010	Chang et al.	2011/0300167 A1	12/2011	McMurry et al.
2010/0086599 A1	4/2010	Huempel et al.	2011/0301087 A1	12/2011	McBride et al.
2010/0092568 A1	4/2010	Lerner et al.	2011/0306579 A1	12/2011	Stein
2010/0105071 A1	4/2010	Laufer et al.	2011/0311592 A1	12/2011	BirBlra
2010/0119585 A1	5/2010	Hille et al.	2011/0312927 A1	12/2011	Nachaegari et al.
2010/0129320 A1	5/2010	Phasivongsa et al.	2011/0312928 A1	12/2011	Nachaegari et al.
2010/0136105 A1	6/2010	Chen et al.	2011/0318405 A1	12/2011	Erwin
2010/0137265 A1	6/2010	Leonard	2011/0318431 A1	12/2011	Gulati
2010/0137271 A1	6/2010	Chen et al.	2012/0009276 A1	1/2012	De Groote
2010/0143420 A1	6/2010	Shenoy et al.	2012/0015350 A1	1/2012	NaBltyan et al.
2010/0143481 A1	6/2010	Shenoy et al.	2012/0021041 A1	1/2012	Rossi et al.
2010/0150993 A1	6/2010	Theobld et al.	2012/0028888 A1	2/2012	Janz et al.
2010/0152144 A1	6/2010	Hermsmeyer	2012/0028910 A1	2/2012	Takruri et al.
2010/0168228 A1	7/2010	Bose et al.	2012/0028936 A1	2/2012	Gloge et al.
2010/0183723 A1	7/2010	Laurent-Applegate et al.	2012/0045532 A1	2/2012	Cohen
2010/0184736 A1	7/2010	Coelingh Bennink et al.	2012/0046264 A1	2/2012	Simes et al.
2010/0190758 A1	7/2010	Fauser et al.	2012/0046518 A1	2/2012	Yoakum et al.
2010/0204326 A1	8/2010	D Souza	2012/0052077 A1	3/2012	Truitt, III et al.
2010/0210994 A1	8/2010	Zarif	2012/0058171 A1	3/2012	De Graaff et al.
2010/0221195 A1	9/2010	Tamarkin et al.	2012/0058962 A1	3/2012	Cumming et al.
2010/0227797 A1	9/2010	Axelson et al.	2012/0058979 A1	3/2012	Keith et al.
2010/0240626 A1	9/2010	Kulkarni et al.	2012/0064135 A1	3/2012	Levin et al.
2010/0247482 A1	9/2010	Cui et al.	2012/0065179 A1	3/2012	Andersson
2010/0247632 A1	9/2010	Dong et al.	2012/0065221 A1	3/2012	Bjbul
2010/0247635 A1	9/2010	Rosenberg et al.	2012/0087872 A1	4/2012	Tamarkin et al.
2010/0255085 A1	10/2010	Liu et al.	2012/0101073 A1	4/2012	Mannion et al.
2010/0273730 A1	10/2010	Hsu et al.	2012/0121517 A1	5/2012	Song et al.
2010/0278759 A1	11/2010	Murad	2012/0121692 A1	5/2012	Xu et al.
2010/0279988 A1	11/2010	Setiawan et al.	2012/0122829 A1	5/2012	Taravella et al.
2010/0291191 A1	11/2010	Shoichet et al.	2012/0128625 A1	5/2012	Shalwitz et al.
2010/0292199 A1	11/2010	Leverd et al.	2012/0128654 A1	5/2012	Terpstra et al.
2010/0303825 A9	12/2010	SirBlsku	2012/0128683 A1	5/2012	Shantha
2010/0312137 A1	12/2010	Gilmour et al.	2012/0128733 A1	5/2012	Perrin et al.
2010/0316724 A1	12/2010	Whitfield et al.	2012/0128777 A1	5/2012	Keck et al.
2010/0322884 A1	12/2010	Dipietro et al.	2012/0129773 A1	5/2012	Geier et al.
2010/0330168 A1	12/2010	Gicquel et al.	2012/0129819 A1	5/2012	Vancaillie et al.
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0136013 A1	5/2012	Li et al.
2011/0039814 A1	2/2011	Huatan et al.	2012/0142645 A1	6/2012	Marx
2011/0053845 A1	3/2011	Levine et al.	2012/0148670 A1	6/2012	Kim et al.
2011/0066473 A1	3/2011	Bernick et al.	2012/0149748 A1	6/2012	Shanler et al.
2011/0076775 A1	3/2011	Stewart et al.	2012/0172343 A1	7/2012	Lindenthal et al.
2011/0076776 A1	3/2011	Stewart et al.	2012/0184515 A1	7/2012	Klar et al.
2011/0086825 A1	4/2011	Chatroux	2012/0209721 A1	10/2012	Weng et al.
2011/0087192 A1	4/2011	Uhland et al.	2012/0277249 A1	11/2012	Andersson et al.
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0277727 A1	11/2012	Doshi et al.
2011/0098258 A1	4/2011	Masini Eteve et al.	2012/0283671 A1	11/2012	ShiBlta et al.
2011/0098631 A1	4/2011	McIntyre et al.	2012/0295911 A1	11/2012	Mannion et al.
2011/0104268 A1	5/2011	Pachot et al.	2012/0301517 A1	11/2012	Zhang et al.
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	2012/0301538 A1	11/2012	Gordon Beresford et al.
2011/0130372 A1	6/2011	Agostinacchio et al.	2012/0302535 A1	11/2012	Caufriez et al.
2011/0135719 A1	6/2011	Besins et al.	2012/0316130 A1	12/2012	Hendrix

US 11,110,099 B2

Page 9

(56)	References Cited		
U.S. PATENT DOCUMENTS			
2012/0316496 A1	12/2012 Hoffmann et al.	2014/0024590 A1	1/2014 Weidhaas et al.
2012/0321579 A1	12/2012 Edelson et al.	2014/0031289 A1	1/2014 Song et al.
2012/0322779 A9	12/2012 Voskuhl	2014/0031323 A1	1/2014 Perez
2012/0328549 A1	12/2012 Edelson et al.	2014/0066416 A1	3/2014 Leunis et al.
2012/0329738 A1	12/2012 Liu	2014/0072531 A1	3/2014 Kim et al.
2013/0004619 A1	1/2013 Chow et al.	2014/0079686 A1	3/2014 Prouty et al.
2013/0011342 A1	1/2013 Tamarkin et al.	2014/0088051 A1	3/2014 Bernick et al.
2013/0017239 A1	1/2013 Viladot Petit et al.	2014/0088058 A1	3/2014 Maurizio
2013/0022674 A1	1/2013 Dudley et al.	2014/0088059 A1	3/2014 Perumal et al.
2013/0023505 A1	1/2013 Garfield et al.	2014/0094426 A1	4/2014 Drummond et al.
2013/0023823 A1	1/2013 Simpson et al.	2014/0094440 A1	4/2014 Bernick et al.
2013/0028850 A1	1/2013 Tamarkin et al.	2014/0094441 A1	4/2014 Bernick et al.
2013/0029947 A1	1/2013 Nachaegari et al.	2014/0099362 A1	4/2014 Bernick et al.
2013/0029957 A1	1/2013 Giliyar et al.	2014/0100159 A1	4/2014 Conrad
2013/0045266 A1	2/2013 Choi et al.	2014/0100204 A1	4/2014 Bernick et al.
2013/0045953 A1	2/2013 Sitruk Ware et al.	2014/0100205 A1	4/2014 Bernick et al.
2013/0059795 A1	3/2013 Lo et al.	2014/0100206 A1	4/2014 Bernick et al.
2013/0064897 A1	3/2013 Binay	2014/0113889 A1	4/2014 Connor et al.
2013/0072466 A1	3/2013 Choi et al.	2014/0127185 A1	5/2014 Stein et al.
2013/0084257 A1	4/2013 Ishida et al.	2014/0127280 A1	5/2014 Duesterberg et al.
2013/0085123 A1	4/2013 Li et al.	2014/0127308 A1	5/2014 Opara et al.
2013/0089574 A1	4/2013 Schmidt Gollwitzer et al.	2014/0128798 A1	5/2014 Janson et al.
2013/0090318 A1	4/2013 Ulmann et al.	2014/0148491 A1	5/2014 Valia et al.
2013/0102781 A1	4/2013 Bevill et al.	2014/0186332 A1	7/2014 Ezrin et al.
2013/0108551 A1	5/2013 Langereis et al.	2014/0187487 A1	7/2014 Shoichet et al.
2013/0116215 A1	5/2013 Coma et al.	2014/0193523 A1	7/2014 Henry
2013/0116222 A1	5/2013 Arnold et al.	2014/0194396 A1	7/2014 Li et al.
2013/0122051 A1	5/2013 Abidi et al.	2014/0206616 A1	7/2014 Ko et al.
2013/0123175 A1	5/2013 Hill et al.	2014/0213565 A1	7/2014 Bernick et al.
2013/0123220 A1	5/2013 Queiroz	2014/0329783 A1	11/2014 Bernick et al.
2013/0123351 A1	5/2013 Dewitt	2014/0370084 A1	12/2014 Bernick et al.
2013/0129818 A1	5/2013 Bernick et al.	2014/0371182 A1	12/2014 Bernick et al.
2013/0131027 A1	5/2013 Pakkalin et al.	2014/0371183 A1	12/2014 Bernick et al.
2013/0131028 A1	5/2013 Snyder et al.	2014/0371184 A1	12/2014 Bernick et al.
2013/0131029 A1	5/2013 Bikker et al.	2015/0031654 A1	1/2015 Amadio
2013/0149314 A1	6/2013 Bullerdiek et al.	2015/0045335 A1	2/2015 Bernick et al.
2013/0164225 A1	6/2013 Tamarkin et al.	2015/0133421 A1	5/2015 Bernick et al.
2013/0164346 A1	6/2013 Lee et al.	2015/0148323 A1	5/2015 Bernick et al.
2013/0165744 A1	6/2013 Carson et al.	2015/0164789 A1	6/2015 Bernick et al.
2013/0178452 A1	7/2013 King	2015/0224117 A1	8/2015 Bernick et al.
2013/0183254 A1	7/2013 Zhou et al.	2015/0224118 A1	8/2015 Bernick et al.
2013/0183325 A1	7/2013 Bottoni et al.	2015/0297733 A1	10/2015 Oberegger et al.
2013/0189193 A1	7/2013 Tamarkin et al.	2015/0302435 A1	10/2015 Bernick et al.
2013/0189196 A1	7/2013 Tamarkin et al.	2015/0342963 A1	12/2015 Bernick et al.
2013/0189230 A1	7/2013 Shoichet et al.	2015/0352126 A1	12/2015 Bernick et al.
2013/0189368 A1	7/2013 Mosqueira et al.	2015/0359737 A1	12/2015 Bernick et al.
2013/0210709 A1	8/2013 McMurry et al.	2016/0030449 A1	2/2016 Persicaner et al.
2013/0216550 A1	8/2013 Penninger et al.	2016/0213685 A1	7/2016 Bernick et al.
2013/0216596 A1	8/2013 Viladot Petit et al.	2017/0056418 A1	3/2017 Thorsteinsson et al.
2013/0224177 A1	8/2013 Kim et al.	2017/0216310 A1	8/2017 Mirkin et al.
2013/0224257 A1	8/2013 Sah et al.	2017/0281645 A1	10/2017 Shadiack et al.
2013/0224268 A1	8/2013 Alam et al.	2017/0281646 A1	10/2017 Inskeep et al.
2013/0224300 A1	8/2013 Maggio	2017/0281647 A1	10/2017 Shadiack et al.
2013/0225412 A1	8/2013 Sardari Lodriche et al.	2017/0281776 A1	10/2017 Shadiack et al.
2013/0225542 A1	8/2013 Poegh et al.	2018/0161343 A1	6/2018 Mirkin et al.
2013/0226113 A1	8/2013 Schumacher et al.	2018/0161344 A1	6/2018 Mirkin et al.
2013/0243696 A1	9/2013 Wang et al.	2018/0161345 A1	6/2018 Bernick et al.
2013/0245253 A1	9/2013 Marx et al.	2018/0221389 A1	8/2018 Amadio et al.
2013/0245570 A1	9/2013 Jackson	2018/0280410 A1	10/2018 Amadio et al.
2013/0261096 A1	10/2013 Merian et al.	2018/0289723 A1	10/2018 Bernick et al.
2013/0266645 A1	10/2013 Becker et al.	2019/0022107 A1	1/2019 Mirkin et al.
2013/0267485 A1	10/2013 Da Silva Maia Filho	2019/0046542 A1	2/2019 Bernick et al.
2013/0273167 A1	10/2013 Lee et al.	2019/0070197 A1	3/2019 Amadio et al.
2013/0274211 A1	10/2013 Burman et al.	2019/0142844 A1	5/2019 Bernick et al.
2013/0280213 A1	10/2013 Voskuhl	2019/0247401 A1	8/2019 Amadio et al.
2013/0316374 A1	11/2013 Penninger et al.	2019/0314386 A1	10/2019 Bernick et al.
2013/0317065 A1	11/2013 Tatani et al.	2019/0343771 A1	11/2019 Mirkin et al.
2013/0317315 A1	11/2013 Lu et al.	2019/0343845 A1	11/2019 Bernick et al.
2013/0324565 A1	12/2013 Li et al.	2019/0358243 A1	11/2019 Mirkin et al.
2013/0331363 A1	12/2013 Li et al.	2020/0069700 A1	3/2020 Bernick et al.
2013/0338122 A1	12/2013 Bernick et al.	2020/0147104 A1	5/2020 Bernick et al.
2013/0338123 A1	12/2013 Bernick et al.	2020/0171050 A1	6/2020 Bernick et al.
2013/0338124 A1	12/2013 Li et al.	2020/0281938 A1	9/2020 Bernick et al.
2013/0345187 A1	12/2013 Rodriguez Oquendo		
2014/0018335 A1	1/2014 Tatani et al.		

US 11,110,099 B2

Page 10

(56)	References Cited				
	U.S. PATENT DOCUMENTS				
2020/0281941 A1	9/2020 Bernick et al.	WO	2001087276	11/2001	
2020/0323881 A1	10/2020 Bernick et al.	WO	WO 2001091757 A1	12/2001	
	FOREIGN PATENT DOCUMENTS				
CA 2612380 A1	12/2006	WO	2002007700	1/2002	
CN 102258455 A	11/2011	WO	2002011768	2/2002	
EP 0261429 A1	3/1988	WO	2002022132	3/2002	
EP 0275716 A1	7/1988	WO	2002040008	5/2002	
EP 0279977 A2	8/1988	WO	2002041878	5/2002	
EP 0622075 A1	11/1994	WO	2002053131	7/2002	
EP 0750495 B1	1/1997	WO	2002078602	10/2002	
EP 0785211 A1	7/1997	WO	2002078604	10/2002	
EP 0785212 A1	7/1997	WO	2003028667	4/2003	
EP 0811381 A1	12/1997	WO	2003041718	5/2003	
EP 904064 A1	3/1999	WO	2003041741	5/2003	
EP 0813412 B1	12/1999	WO	2003068186	8/2003	
EP 1300152 A1	4/2003	WO	2003077923	9/2003	
EP 1094781 B1	7/2008	WO	2003082254	10/2003	
EP 2191833 A1	6/2010	WO	2003092588	11/2003	
GB 452238 A	8/1936	WO	2004014397 A1	2/2004	
GB 720561 A	12/1954	WO	2004014432	2/2004	
GB 848881 A	9/1960	WO	2004017983	3/2004	
GB 874368 A	8/1961	WO	2004032897	4/2004	
GB 1589946 A	5/1981	WO	WO 2004032942 A1	4/2004	
IN 2005KOL00053	8/2005	WO	2004052336	6/2004	
IN 216026	3/2008	WO	2004054540	7/2004	
IN 244217	11/2010	WO	WO 2004110402 A1	12/2004	
JP H 2-207024 A	8/1990	WO	WO 2004110408 A2	12/2004	
JP H 2-264725 A	10/1990	WO	2005027911	3/2005	
JP H 04-503810 A	7/1992	WO	2005030175	4/2005	
JP H 10-251116 A	9/1998	WO	2005081825	9/2005	
JP H 11-514994 A	12/1999	WO	2005087194	9/2005	
JP 2002510336 A	4/2002	WO	2005087199	9/2005	
JP 2006513182 A	4/2006	WO	2005105059	11/2005	
RU 2155582 C2	9/2000	WO	2005115335	12/2005	
RU 2449796 C2	2/2006	WO	2005120470	12/2005	
RU 2317813 C2	2/2008	WO	2005120517	12/2005	
WO 1990010425 A1	9/1990	WO	20060113369	2/2006	
WO 1990011064	10/1990	WO	2006034090	3/2006	
WO 1993017686	9/1993	WO	2006036899	4/2006	
WO 1994022426	10/1994	WO	2006053172	5/2006	
WO WO 1995005807 A1	3/1995	WO	2006105615	10/2006	
WO 1995030409	11/1995	WO	2006113505	10/2006	
WO 1996009826	4/1996	WO	2006138686	12/2006	
WO 1996019975	7/1996	WO	2006138735	12/2006	
WO 1996030000	10/1996	WO	2007045027	4/2007	
WO 1997005491	2/1997	WO	WO 2007076144 A2	7/2007	
WO 1997043989	11/1997	WO	2007103294	9/2007	
WO WO 199740823 A1	11/1997	WO	2007120868	10/2007	
WO 1998010293	3/1998	WO	2007123790	11/2007	
WO 1998032465	7/1998	WO	2007124250	11/2007	
WO WO 1998041217 A1	9/1998	WO	2007144151	12/2007	
WO 1998051280	11/1998	WO	2008049516	5/2008	
WO 1999022680 A1	5/1999	WO	2008152444	12/2008	
WO 1999032072	7/1999	WO	2009002542	12/2008	
WO 1999039700	8/1999	WO	2009036311	3/2009	
WO 1999042109	8/1999	WO	2009040818	4/2009	
WO 1999043304	9/1999	WO	2009069006	6/2009	
WO 1999048477	9/1999	WO	2009098072	8/2009	
WO 1999053910	10/1999	WO	2009133352	11/2009	
WO WO 1999052528 A1	10/1999	WO	2010033188	3/2010	
WO WO 1999055333 A1	11/1999	WO	2010146872	12/2010	
WO 1999063974	12/1999	WO	2011000210	1/2011	
WO WO 1999062497 A1	12/1999	WO	2011073995	6/2011	
WO 2000001351	1/2000	WO	2011120084	10/2011	
WO 2000006175	2/2000	WO	2011128336	10/2011	
WO 2000038659	6/2000	WO	2012009778	1/2012	
WO 2000045795	8/2000	WO	2012024361	2/2012	
WO 2000050007	8/2000	WO	2012055814 A1	5/2012	
WO 2000059577	10/2000	WO	2012055840 A1	5/2012	
WO 2000076522	12/2000	WO	2012065740	5/2012	
WO 2001037808	5/2001	WO	2012098090 A1	7/2012	
WO 2001054699	8/2001	WO	2012116277 A1	8/2012	
WO 2001060325	8/2001	WO	2012118563 A2	9/2012	
		WO	2012120365 A1	9/2012	
		WO	2012127501 A2	9/2012	
		WO	2012156561 A1	11/2012	
		WO	2012156822 A1	11/2012	
		WO	2012158483 A2	11/2012	

US 11,110,099 B2

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(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2012166909	A1	12/2012
WO	2012170578	A1	12/2012
WO	2013011501	A1	1/2013
WO	2013025449	A1	2/2013
WO	2013028639	A1	2/2013
WO	2013035101	A1	3/2013
WO	2013044067	A1	3/2013
WO	2013045404	A2	4/2013
WO	2013059285	A1	4/2013
WO	2013063279	A1	5/2013
WO	2013064620	A1	5/2013
WO	2013071281	A1	5/2013
WO	WO 2013078422	A2	5/2013
WO	2013088254		6/2013
WO	2013102665	A1	7/2013
WO	2013106437	A1	7/2013
WO	2013112947	A1	8/2013
WO	2013113690		8/2013
WO	2013124415	A1	8/2013
WO	2013127727	A1	9/2013
WO	2013127728	A1	9/2013
WO	2013144356	A1	10/2013
WO	2013149258	A2	10/2013
WO	2013158454	A2	10/2013
WO	2013170052	A1	11/2013
WO	2013178587	A1	12/2013
WO	2013181449	A1	12/2013
WO	2013192248		12/2013
WO	2013192249		12/2013
WO	2013192250		12/2013
WO	2013192251		12/2013
WO	2014001904	A1	1/2014
WO	2014004424	A1	1/2014
WO	2014009434	A1	1/2014
WO	2014018569	A1	1/2014
WO	2014018570	A1	1/2014
WO	2014018571	A2	1/2014
WO	2014018856	A1	1/2014
WO	2014018932	A2	1/2014
WO	2014031958	A1	2/2014
WO	2014041120	A1	3/2014
WO	2014052792	A1	4/2014
WO	2014056897	A1	4/2014
WO	2014066442	A2	5/2014
WO	2014074846	A1	5/2014
WO	2014076231	A1	5/2014
WO	2014076569	A2	5/2014
WO	2014081598	A1	5/2014
WO	2014086739	A1	6/2014
WO	2014093114	A1	6/2014
WO	2014104784	A1	7/2014
WO	WO 2015179782	A1	11/2015
WO	WO 2016018993	A1	2/2016

OTHER PUBLICATIONS

- Center for Drug Evaluation and Research, Application No. NDA 19-781, Clinical Pharmacology and Biopharmaceutics Reviews, 1998, 59 pages, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/19781.cfm.
- Chambin, O and Jannin, V., "Interest of Multifunctional Lipid Excipients: Case of Gelucire® 44/14," *Drug Development and Industrial Pharmacy*, 31(6):527-534, Informa Healthcare, England (Jul. 2005).
- Cho, Y.A. et al., "Transdermal Delivery of Ketorolac Tromethamine: Effects of Vehicles and Penetration Enhancers," *Drug Development and Industrial Pharmacy*, 30(6):557-564, Marcel Dekker, Inc., United States (2004).
- Cincinelli, E., et al., "First uterine pass effect is observed when estradiol is placed in the upper but not lower third of the vagina," *Fertility and Sterility*, 81(5): 1414-1416, Elsevier Inc., Netherlands (2004).
- Cincinelli, E., "Intravaginal oestrogen and progestin administration: advantages and disadvantages," *Best Practices & Research Clinical Obstetrics and Gynaecology*, 22(2): 391-405, Elsevier, Netherlands (2008).

- Co-pending U.S. Appl. No. 16/833,186 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/833,188 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/833,213 Inventor, Bernick, B.A., filed Mar. 27, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/834,780 Inventor, Bernick, B.A., filed Mar. 30, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/834,844 Inventor, Bernick, B.A., filed Mar. 30, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/837,929, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/837,933, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/837,937, Inventor, Bernick, B.A., filed Apr. 1, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/875,030 Inventor, Bernick, B.A., filed May 15, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/885,088 Inventor, Bernick, B.A., filed May 27, 2020 (Not Published).
- Co-pending U.S. Appl. No. 16/855,094 Inventor, Bernick, B.A., filed May 27, 2020 (Not Published).
- Crandall, C, "Vaginal Estrogen Preparations: a Review of Safety and Efficacy for Vaginal Atrophy," *Journal of Women's Health*, 11(10):857-877, Mary Ann Liebert, Inc, United States, (Dec. 2002).
- Cremer Care, Miglyol® 810,812 INCI: Caprylic/Capric Triglyceride, Cremer OLEO GmbH & Co. KG, pp. 1-7, available at http://s3.amazonaws.com/petercremerma/products/spec_sheets/159/339/301/original/MIGLYOL_810_812_TDS.pdf?1389204445, Mar. 2013.
- De Vries, T.P.G.M., et al, Guide to Good Prescribing: A Practical Manual, Essential Medicines and Health Products Information Portal, World Health Organization, Annex 3 ("How to explain the use of some dosage forms"), Checklist 11 ("Vaginal tablet without applicator") available at <http://apps.who.int/medicinedocs/en/d/Jwhozip23e/7.3.11.html>, 2 pages, 1994.
- Ettinger, B., et al., "Measuring symptom relief in studies of vaginal and vulvar atrophy: the most bothersome symptom approach," *Menopause*, 15(5): 885-889, The North American Menopause Society, United States (2008).
- Eugster-Hausmann, M., et al., "Minimized estradiol absorption with ultra-low-dose 10 µg 17β-estradiol vaginal tablets," *Climacteric*, 13:219-227, International Menopause Society, United Kingdom (2010).
- Extended European Search Report for EP Application No. EP 13807188.1, Munich, Germany, dated Nov. 23, 2015, 7 pages.
- Garad S., et al., "Preclinical Development for Suspensions," Chapter 5, A.K. Kulshreshtha et al. (eds.), *Pharmaceutical Suspensions: From Formulation Development to Manufacturing*, Springer, New York, pp. 127-176 (2010).
- Hitchcock, C. L., et al., "Oral micronized progesterone for vasomotor symptoms—a placebo-controlled randomized trial in healthy postmenopausal women," *Menopause: The Journal of The North American Menopause Society*, 19(8):886-893, The North American Menopause Society, United States, (2012).
- Holm, R., et al., "Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides," *European Journal of Pharmaceutical Sciences* 20: 91-97, Elsevier, Netherlands (2003).
- Hosmer, J., et al., "Microemulsions Containing Medium-Chain Glycerides as Transdermal Delivery Systems for Hydrophilic and Hydrophobic Drugs," *AAPS PharmSciTech*, 10(2): 589-596, American Association of Pharmaceutical Scientists, United States (2009).
- Karande, P., et al., "Enhancement of transdermal drug delivery via synergistic action of chemicals," *Biochimica et Biophysica Acta*, 1788: 2362-2373, Elsevier, Netherlands (2009).
- Kingsburg, S.A., et al., "Treating dyspareunia caused by vaginal atrophy: a review of treatment options using vaginal estrogen therapy," *International Journal of Women's Health*, 1:105-111, Dove Medical Press Ltd., United Kingdom (2009).

US 11,110,099 B2

Page 12

(56)

References Cited

OTHER PUBLICATIONS

- Lopes, L. B., et al., "Enhancement of transdermal delivery of progesterone using medium-chain mono and diglycerides as skin penetration enhancers," *Pharmaceutical Development and Technology*, 14(5): 524-529, Informa UK Ltd., United Kingdom (2009).
- Mac Bride, M.B., et al., "Vulvovaginal Atrophy," *Mayo Clinic Proceedings*, 85(1): 87-94, Mayo Foundation for Medical Education and Research, United States (2010).
- March, C. M. et al., "Roles of Estradiol and Progesterone in Eliciting the Midcycle Luteinizing Hormone and Follicle-Stimulating Hormone Surges," *The Journal of Clinical Endocrinology & Metabolism*, 49(4): 507-513, The Endocrine Society, United States (1979).
- Martelli, M.E., Vaginal Medicine Administration, The Gale Encyclopedia of Nursing and Allied Health, Gale Group, pp. 2542-2543 (2002).
- Mirkin, S., et al., "The Replenish Trial: Evaluating TX-001HR ,The First Combination 17 (3-Estradioi/Natural Progesterone Capsule using SYMBODA™ technology), a new option for the treatment of menopausal symptoms," 14th World Congress on Menopause, May 1-4, 2014 in Cancun, Mexico, Therapeutics MD, 1 page.
- Monti, D. et al., "Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin," *International Journal of Pharmaceutics*, 237:209-24, Elsevier, Netherlands (2002).
- Non-Final Office Action dated Feb. 1, 2016 in U.S. Appl. No. 14/690,955, Inventors, Bernick, B.A., dated Apr. 20, 2015, 9 pages.
- Final Office Action dated Nov. 9, 2016, in U.S. Appl. No. 14/690,955, Inventors, Bernick, B.A., dated Apr. 20, 2015, 12 pages.
- Non-Final Office Action dated Jul. 14, 2014 in U.S. Appl. No. 14/690,955, Inventors, Bernick, B.A., dated Apr. 20, 2015, 14 pages.
- Non-Final Office Action dated Apr. 2, 2020 in U.S. Appl. No. 15/999,040, Inventors, Bernick, B.A., dated Aug. 16, 2018, 10 pages.
- Pachman, D.R., et al., "Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions," *International Journal of Women's Health*, Dove Medical Press Ltd., United Kingdom, (2010).
- Pickar, J.H., et al., "Pharmacokinetics of the First Combination 17B-Estradioi/Progesterone Capsule in Clinical Development for Hormone Therapy," Presented at the 24th annual meeting of the North American Menopause Society, Oct. 9-12, 2013 in Dallas, TX, 1 page.
- Potluri, P. and Betageri, G.V., "Mixed-micellar proliposomal systems for enhanced oral delivery of progesterone," *Drug Delivery*, 13(3): 227-232, Taylor & Francis Group, LLC, United Kingdom (2006).
- Prometrium® (progesterone, USP) prescribing information (Jun. 2009) FDA Label, 33 pages.
- Rao, R. et al., "The Affect of Capmul, Labrafil and Transcutol on Progesterone 100 Mg Soft Capsules Bioavailability in Indian Healthy Adult Postmenopausal Female Subjects Under Fasting Conditions," *Bioequivalence & Bioavailability*, 7(2):095-107, Medwin Publishers, United States (2015).
- Regidor, P., "Progesterone in Peri- and Postmenopause: A Review," *Geburtshilfe Frauenheilkd*, 74(11): 995-1002, Georg Thieme Verlag KG Stuttgart, New York (2014).
- Rioux, J.E., et al., "17 β-Estradiol Vaginal Tablet Versus Conjugated Equine Estrogen Vaginal Cream to Relieve Menopausal Atrophic Vaginitis," *Menopause: The Journal of The North American Menopause Society*, 7(3): 156-161, The North American Menopause Society, United States (2000).
- Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences* 11(3):42-49, Niper, India (2010).
- Simon, J.A., et al., "The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone," *Fertility and Sterility*, 60(1):26-33, Elsevier for the American Society for Reproductive Medicine, United States (1993).
- Simon, J. A. et al., "A vaginal estradiol softgel capsule, TX-004HR, has negligible to very low systemic absorption of estradiol: Efficacy and pharmacokinetic data review," *Maturitas*, 99: 51-58, Elsevier, Netherlands (2017).
- Sofi, S. H. et al., "Gelucire: A Versatile Formulation Excipient," *IJPPR Human*, 10(3): 55-73, (2017).
- Stefanick, M.L., "Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration," *The American Journal of Medicine* 118(12B): 64S-73S, Elsevier, Netherlands (2005).
- Tang, O.S., et al., "Pharmacokinetics of different routes of administration of misoprostol," *Human Reproduction*, 17(2):332-226, European Society of Human Reproduction and Embryology, Belgium (2002).
- Vagifem® (estradiol vaginal tablets) prescribing information (Nov. 2009) FDA Label, 14 pages.
- Wang, H., et al., "Pharmacokinetics of hard micronized progesterone capsules via vaginal or oral route compared with soft micronized capsules in healthy postmenopausal women: a randomized open-label clinical study," *Drug Des Devel Ther.*, 13: 2475-2482, Dove Medical Press Ltd., United Kingdom (2019).
- Abbas et al., Regession of endometrial implants treated with vitamin D₃ in a rat model of endometriosis, *European J of Pharma*, 715 (2013) 72-75, Elsevier.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, Capmul PG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Acarturk, Fusun, Mucoadhesive Vaginal Drug Delivery System, Recent Patents on Drug Delivery & Formulation, 2009, vol. 3, pp. 193-195.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Huta crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-F10508-008, CD spectra of pharmaceuticals substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Araya-Siblja et. al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Araya-Siblja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Siblja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Siblja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Araya-Siblja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, *Menopause: The Journal of the North American Menopause Society*, vol. 22, No. 77, pp. 1-11 (2015).

US 11,110,099 B2

Page 13

(56)

References Cited

OTHER PUBLICATIONS

- Archer et al., Estrate® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, *Advances in Therapy®*, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, *Yale J Biology and Medicine*, vol. 35, Feb. 1963, pp. 329-340.
- Azeem, Adnan et al., Microemulsions as a Surrogate Carrier for Dermal Drug Delivery, *Drug Development and Industrial Pharmacy*, May 2000, vol. 35, No. 5, pp. 525-547 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/03639040802448646>.
- Azure Pharma, Inc.. Elestrin™—Estradiol Gel, Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, Aug. 2009.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, *SSCI, Division of Aptuit, Poster No. R6247, West Lafayette*.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, *Current Medicinal Chemistry*, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, *Biology of Reproduction* 52, 1327-1333 (1995).
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani Bhagu R. et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," *J Clin Endocrinol Metab*, Mar. 2012, 97(3):756-759.
- Bhavnani et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER α and ER β , *Endocrinology*, Oct. 2008, 149(10):4857-4870.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductiveaged female subjects, *Fertility and Sterility* # vol. 94, No. 4, Sep. 2010, Elsevier.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index> [Feb. 3, 2014 1:37:50 PM].
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moleculaire de l'Oestradiol Hemihydrate, *Acta Cryst.*, B28 pp. 560, 1972, Bis(dimethyl-o-thiolophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Molcculaire de la Progesterone C21H30O2, *Acta Cryst.*, B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.
- ChemPro, Top-Notch Technology in Production of Oils and Fats, *Chempro-Edible-Oil-Refining-ISO-TUV-Austria*.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, *J Clin Oncol* 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008: 59:344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance , *Contact Dermatitis*, 71, 264-272, 2014.
- Chun et al., Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles . . . , *J. Kor. Pharm. Sci.*, vol. 35, No. 3, pp. 173-177 (2005).
- Cicinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, Mar. 2000, pp. 403-406.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, *Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div.*, vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Committee Opinion, Incidentally Detected Short Cervical Length, *Committee of Obstetric Practice, Obstetrics & Gynecology, ACOG*, vol. 119, No. 4, Apr. 2012, pp. 879-882.
- Commodari, Fernando, Comparison of 17 β -estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, *Research Letters*, Apr. 25, 1998.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," *Southern Medical Journal*, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Corn Refiners Association, *Corn Oil*, 5th Edition, Washington, D.C., 2006.
- Critchley et al., Estrogen Receptor β , But Not Estrogen Receptor α , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Dauqan, Eqbl M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE), vol. 14, 2011, IACSIT Press, Singapore.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Diramio, Jackie A., Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs, *Masters of Science Thesis, University of Georgia, Athens, Georgia*, 2002, 131 pages.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *SciFinder, Pharmaceutica Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.

US 11,110,099 B2

Page 14

(56)

References Cited

OTHER PUBLICATIONS

- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Estradiol, The Merck Index Online, Royal Society of Chemistry, <https://www.rsc.org/Merck-Index/monograph/mono1500003758/estradiol?#q=uauthorize>.
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GMBH, 2010, 28 pages.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, PiracicaB1, Braz.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene Based on exposure and effect data, *Contact Dermatitis* 1990; 23: 341-345.
- Fotherby, K., Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, *Contraception*, 1996; 54:59-69.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.*(2013), Elsevier.
- Fuchs et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Cutis*. Jun. 2003;71(6):481-8.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gäfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Ganam-Quintanar et al., Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss, *International Journal of Pharmaceutics*, vo. 147, No. 2, Feb. 28, 1997, pp. 165-171 (abstract only).
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/B1ck-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Giron-Forest, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Glaser et al., Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al., Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Gurney, E.P. et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J.Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane Barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- Haner, Barbara, Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hargrove et al., Menopausal Hormone Replacement Therapy with Continuous Daily Oral Micronize Estradiol and Progesterone, *Obstet Gynecol*, vol. 73, No. 4, Apr. 1989, pp. 606-612.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Herman, Anna et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, pp. 1-13.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hostynek, JJ, Predicting absorption of fragrance chemicals through human skin, *j. Soc.C osmeCt. hem.*,4 6, 221-229 (Jul./Aug. 1995).

US 11,110,099 B2

Page 15

(56)

References Cited

OTHER PUBLICATIONS

- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Humberstone, Andrew et al., "Lipid-based vehicles for the oral delivery of poorly water soluble drugs," *Advanced Drug Delivery Reviews*, 25 (1997) 103-128.
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, *Journal of Cerebral Blood Flow and Metabolism* 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 α -Ethynodiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 β -Estradiol, *JPET* 290(2):740-747, 1999.
- Idder, Salima, et al., Physicochemical properties of Progesterone, *SciFinder*, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johanson, Gunnar, Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester, *Critical Reviews in Toxicology*, 2000, vol. 30, No. 3 , pp. 307-345 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/10408440091159220>.
- Johnson, William S, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, *J Reprod Fert* (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, *Environmental Health Perspectives* • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, *Contact Dermatitis*, 1992: 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, *Ann. Occup. Hyg.*, vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of The North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Blzedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Kincl et al., Increasing Oral Bioavailability of Progesterone by Formulation, *Journal of Steroid Biochemistry*, 1978, vol. 9, pp. 83-84.
- Knuth et al., Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations, *Advanced Drug Delivery Reviews*, vol. 11, No. 1-2, Jul.-Aug. 1993, pp. 137-167 (abstract only).
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.
- Komm et al., Blzedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Korkmaz, Filiz, Byophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of The Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminek, R, et al., EPR Study of the Stable Radical in a γ -Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier (abstract only).
- Kuhnert-Brandstaetter and Grimm. Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen II, *Mikrochimica Acta*, vol. 1, pp. 127-139, 1968.
- Kuhnert-Brandstaetter and Junger and Kofler. Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Kuhnert-Brandstaetter and Kofler. Zur mikroskopischen Identitätsprüfung, und zur Polymorphie der Sexualhormone, *Mikrochimica Acta*, vol. 6, pp. 847-853, 1959.
- Kuhnert-Brandstaetter and Linder. Zur Hydratbildung bei Steroidhormonen, *Sci. Pharm.*, vol. 41(2), pp. 109-116, 1973.
- Kumasaka et al., Effects of Various Forms of Progestin on the the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2), 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol*. Jul. 2011 ; 205(1): e1-e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVV in OB/GYN*, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol*. May 2010 ; 202(5): 455.e1-455.e9.
- Labrie, et al., Intravaginal prosterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skib1, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steriods, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G. et al., Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women, *Maturitas*, The European Menopause Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroid conformation of 17 α - and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lindmark, Tuulikki et al., "Absorption Enhancement through Intracellular Regulation of Tight Junction Permeability by Medium Chain Fatty Acids in Caco-2 Cells," *JPET* 284(1):362-369, 1998.
- Lindmark, Tuulikki et al., "Mechanisms of Absorption Enhancement by Medium Chain Fatty Acids in Intestinal Epithelial Caco-2 Cell Monolayers," *JPET* 275(2):958-964, 1995.

US 11,110,099 B2

Page 16

(56)

References Cited

OTHER PUBLICATIONS

- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Lucy et al., Gonadotropin-releasing hormone at estrus: lutenizing hormone, estradiol, and progesterone during . . . *Biol Reprod* Sep. 1986;35(2):300-311 (abstract only).
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Magness, R.R., et al., Estrone, Estradiol-17 β and Progesterone Concentrations in Uterine Lymph and Systematic Blood throughout the Porcine Estrone Estrous Cycle, *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration by Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Mueck, A.O. et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Ng, Jo-Han et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*,35(9) pp. 1035, 2009.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- NuGen, What is NuGen HP Hair Growth System.
- NuGest900, NuGest 900™.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical application of pregersterone cream to pre-and post-menopausal women, *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Opinion on the Diethylene Glycol Momoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Panay et al., The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy, *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Panchangnula et al., Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol . . . , *J Pharm Pharmacol. Sep.* 1991;43(9):609-614 (abstract only).
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Patel et al., Transdermal Drug Delivery System: A Review, www.thepharmajournal.com, vol. 1, No. 4, 2012, pp. 78-87.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of The North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Position Statement, Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society (NAMS), *Menopause*, vol. 20, No. 9, pp. 888-902.
- Practice Bulletin No. 141, Management of Menopausal Symptoms, *Obstetrics & Gynecology*, ACOG, vol. 123, No. 1, Jan. 2014, pp. 202-216.
- Prajapati Hetal N. et al., "A Comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water Phase Diagram, Solubility Determination and Dispersion Testing for Application in Pharmaceutical Dosage Form Development," *Pharm. Res.* Jan. 2012; 29(1): 285-305. Published online Aug. 23, 2011. doi: 10.1007/s11095-011-0541-3.
- Prajapati Hetal N. et al., "Effect of Difference in Fatty Acid Chain Lengths of Medium-Chain Lipids on Lipid/Surfactant/Water Phase Diagrams and Drug Solubility," *J. Excipients and Food Chem.* 2 (3) 2011:73-88.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol.* Nov. 2008 ; 26(11): 1261-1268.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.

US 11,110,099 B2

Page 17

(56)

References Cited

OTHER PUBLICATIONS

- Product Information Sheet, Body Bllance Cream, Tahitian Noni International, 2013, 1 page.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Progesterone, The Merck Index Online, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches_Pack%20%2028Estradiol%20Hemihydrate%29.html, 2010.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause a Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014, 6: 139-143.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181, 512-520 (2014).
- Rosilio, V. et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *AnnJ Obstet Gynecol*, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010;5 943-954, Dove Press.
- Sallee, Verney L. et al., "Determinants of intestinal mucosal uptake of short- and medium-chain fatty acids and alcohols," *Journal of Lipid Research*, 1973, vol. 14, 475-484.
- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Salole, Eugene G., The physicochemical properties of oestradiol, *Journal of Pharmaceutical & Biomedical Analysis*, vol. 5, No. 7, pp. 635-648, 1987.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, *Climacteric* 2014;17:1-14.
- Sarkar, B1su, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Blse . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Sarpal, K. et al., "Self emulsifying drug delivery systems: a strategy to improve oral bioavailability," *Current Research & Information on Pharmaceuticals Sciences (CRIPS)*, 2010, vol. 11, No. 3, pp. 42-49.
- Sarrel, et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, *American Journal of Public Health, Research and Practice*, e1-e6. Published online ahead of print Jul. 18, 2013.
- Satyanarayana, D. et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The “newer” progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem.Mol. Biol.* (2013), Elsevier.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, *Maturitas* 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, *Fertil Steril*. Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, *Toxicologic Pathology*, 42: 1188-1196, 2014.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Search Report, Extended European Search Report for EP13741053. 6, dated Jul. 1, 2015.
- Search Report, International Search Report for PCT/US12/66406, dated Jan. 24, 2013.
- Search Report, International Search Report for PCT/US13/23309, dated Apr. 9, 2013.
- Search Report, International Search Report for PCT/US13/46442, dated Nov. 1, 2013.
- Search Report, International Search Report for PCT/US13/46443, dated Oct. 31, 2013.
- Search Report, International Search Report for PCT/US13/46444, dated Oct. 31, 2013.
- Search Report, International Search Report for PCT/US13/46445, dated Nov. 1, 2013.
- Search Report, International Search Report for PCT/US14/61811, dated Jan. 21, 2015.
- Search Report, International Search Report for PCT/US15/23041, dated Jun. 30, 2015.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CPLUS DataBlse.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, *Journal of Experimental & Clinical Cancer Research* 2014, 33(1):41, 11 pages.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *Journal of Adolescent Health*, 2003; 32:183-186.
- Shufelt et al., Hormone therapy dose, formulation, route delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, *Menopause: The Journal of The North American Menopause Society*, vol. 21, No. 3, 2014, pp. 1-7, 2013.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, *Pharmaceutical Technology*, Aug. 2014, pp. 28, 30-31.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmapelridge.com/catalog/product/sigma/p7556>.
- Simon et al., Effective Treatment of Vaginal atrophy with an Ultra-low-dose estradiol vaginal tablet, *Obstetrics & Gynecology*, vol. 112, No. 5, Nov. 2008, pp. 1053-1060.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? *Menopause: The Journal of The North American Menopause Society*, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware et al., Progestogens hormonal replacement therapy: new molecules, risks, and benefits, *Menopause: The Journal of The North American Menopause Society*. vol. 9, No. 1, pp. 6-15, 2002.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," *Maturitas* 47 (2004) 277-283.
- Sitruk-Ware, Regine, Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review, *Contraception*, Oct. 1987, vol. 36, No. 4, pp. 373-402.
- Smith et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, *JAMA Internal Medicine*, Published online Sep. 30, 2013, E1-E7. jamanetwork.com.

US 11,110,099 B2

Page 18

(56)

References Cited

OTHER PUBLICATIONS

- Smyth et al., Summary of Toxicological Data, A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats, *Fd Cosmet. Toxicol.* vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Therapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, *Contraception*, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause: The Journal of The North American Menopause Society*, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z. et al., Ethinyl estradiol and 17 β -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, *Contraception* 87 (Jun. 2013) vol. 87, No. 6, pp. 706-727.
- Stanczyk, F.Z., "All progestins are not created equal," *Steroids* 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" *Climacteric* 2014;17 (Suppl 2):8-11.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," *Int J Pharmaceutical Compounding*, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Strickley, Robert T., Solubilizing excipients in oral and injectable formulations, *Pharmaceutical Research* Feb. 2004, vol. 21, Issue 2, pp. 201-230 (abstract only).
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- Struhar, M. et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether(DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, Alternative Medicine Review vol. 12, No. 3, 2007, pp. 259-264.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helveticae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, *Biology of Reproduction* 31, 399-413 (1984).
- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, *Gynecol Endocrinol*, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Thomas, Peter, Characteristics of membrane progestin receptor alpha (mPR α) and progesterone membrane receptor component 1 (PGMRC1) and their roles in mediating rapid progestin actions, *Frontiers in Neuroendocrinology* 29 (2008) 292-312.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010
- Trommer et al., Overcoming the stratum Corneum: The modulation of Skin Penetration, *Skin Pharmacol Physiol* 2006;19:106-121.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- Ueda et al., Topical and Transdermal Drug Products, *Pharmacopeial Forum*, vol. 35(3) [May-Jun. 2009], 750-754.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Certificate—Corn Oil, Lot G0L404, Jul. 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Monographs: Progesterone, USP29, www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html, search done: Feb. 25, 2014.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- U.S. Appl. No. 13/843,428, filed Jul. 2, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/106,655, filed Jun. 19, 2015 Final Office Action.
- U.S. Appl. No. 12/561,515, filed Dec. 12, 2011 Office Action.
- U.S. Appl. No. 12/561,515, filed Oct. 26, 2012 Final Office Action.
- U.S. Appl. No. 12/561,515, filed Jan. 29, 2013_Advisory_Action.
- U.S. Appl. No. 12/561,515, filed Sep. 11, 2013 Notice of Allowance.
- U.S. Appl. No. 13/684,002, filed Mar. 20, 2013_Non-Final_OfficAction.
- U.S. Appl. No. 13/684,002, filed Jul. 16, 2013_Final_OfficAction.
- U.S. Appl. No. 13/684,002, filed Dec. 6, 2013_Notice_of_Accordance.
- U.S. Appl. No. 13/843,362, filed Mar. 16, 2015_Restriction_Requirement.
- U.S. Appl. No. 13/843,428, filed Apr. 14, 2015_Restriction_Requirement.
- U.S. Appl. No. 14/099,545, filed Feb. 18, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,545, filed Jul. 14, 2014_Notice_of_Accordance.
- U.S. Appl. No. 14/099,562, filed Feb. 20, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,562, filed Mar. 27, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,562, filed Jul. 2, 2014_Final_OfficAction.
- U.S. Appl. No. 14/099,562, filed Dec. 10, 2014_Notice_of_Accordance.
- U.S. Appl. No. 14/099,571, filed Mar. 28, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,571, filed Jul. 15, 2014_Notice_of_Accordance.
- U.S. Appl. No. 14/099,582, filed Apr. 29, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,582, filed Jun. 17, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,582, filed Nov. 7, 2014_Notice_of_Accordance.
- U.S. Appl. No. 14/099,582, filed Jan. 22, 2015_Notice_of_Accordance.
- U.S. Appl. No. 14/099,598, filed May 13, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,598, filed Jul. 3, 2014_Non-Final_OfficAction.
- U.S. Appl. No. 14/099,598, filed Dec. 10, 2014_Notice_of_Accordance.

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(56)

References Cited

OTHER PUBLICATIONS

- U.S. Appl. No. 14/099,612, filed Mar. 20, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,612, filed Oct. 30, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,612, filed Nov. 26, 2014_Note_of_Allowance.
- U.S. Appl. No. 14/099,623, filed Mar. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/099,623, filed Jul. 18, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/099,623, filed Dec. 15, 2014_Note_of_Allowance.
- U.S. Appl. No. 14/106,655, filed Jul. 3, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/106,655, filed Dec. 8, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/125,554, filed Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/125,554, filed Apr. 14, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/136,048, filed Nov. 4, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/136,048, filed Mar. 12, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,814, filed Oct. 1, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,814, filed Feb. 13, 2015_Note_of_Allowance.
- U.S. Appl. No. 14/475,864, filed Oct. 2, 2014_Non-Final_Office_Action.
- U.S. Appl. No. 14/475,864, filed Feb. 11, 2015_Note_of_Allowance.
- U.S. Appl. No. 14/476,040, filed Mar. 26, 2015_Restriction_Requirement.
- U.S. Appl. No. 14/521,230, filed Dec. 5, 2014_Restriction_Requirement.
- U.S. Appl. No. 14/521,230, filed Feb. 18, 2015_Non-Final_Office_Action.
- U.S. Appl. No. 14/624,051, filed Apr. 7, 2015_Non-Final_Office_Action.
- Utian, Wulf H. et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens, *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.
- Voegtlne et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.
- Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.
- Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role for the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).
- Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforb.es/1LIUm1V> on Feb. 23, 2015, 3 pages.
- Whitehead et al., Absorption and metabolism of oral progesterone, *The British Medical Journal*, vol. 280, No. 6217 (Mar. 22, 1980), pp. 825-827, BMJ Publishing Group.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Wood et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, *Breast Cancer Res Treat* (2007) 101:125-134.
- Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
- Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).
- Yalkowsky, Samuel H. & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, *Handbook of Acqueous Solubility Data, Solutions*, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.
- Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, *Script*, ZRT Laboratory, pp. 4-5. http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid.
- Non-Final Office Action dated Nov. 13, 2020 in U.S. Appl. No. 15/999,040, Inventors, Bernick, B.A., dated Aug. 16, 2018, 7 pages.

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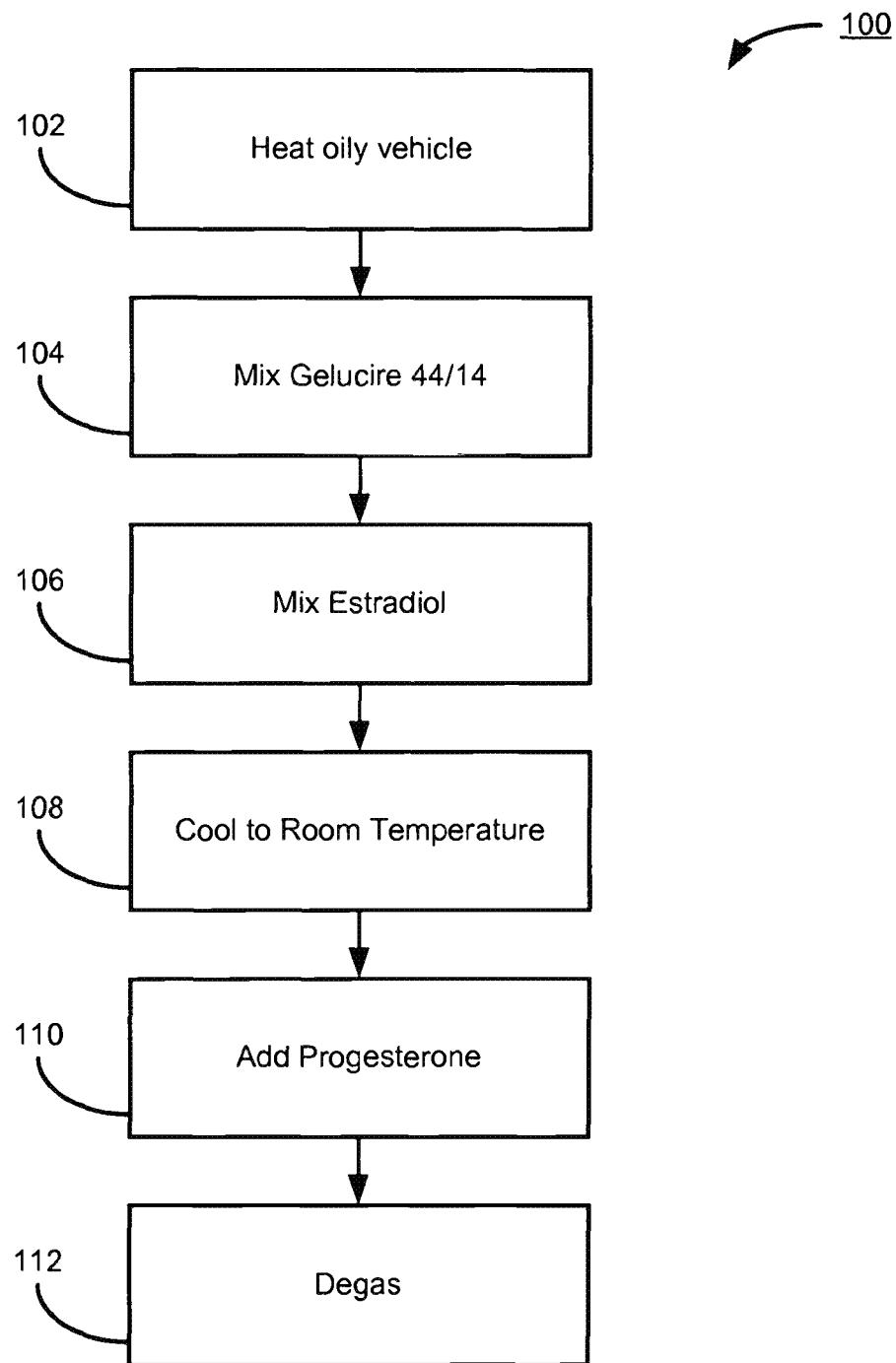


FIG. 1

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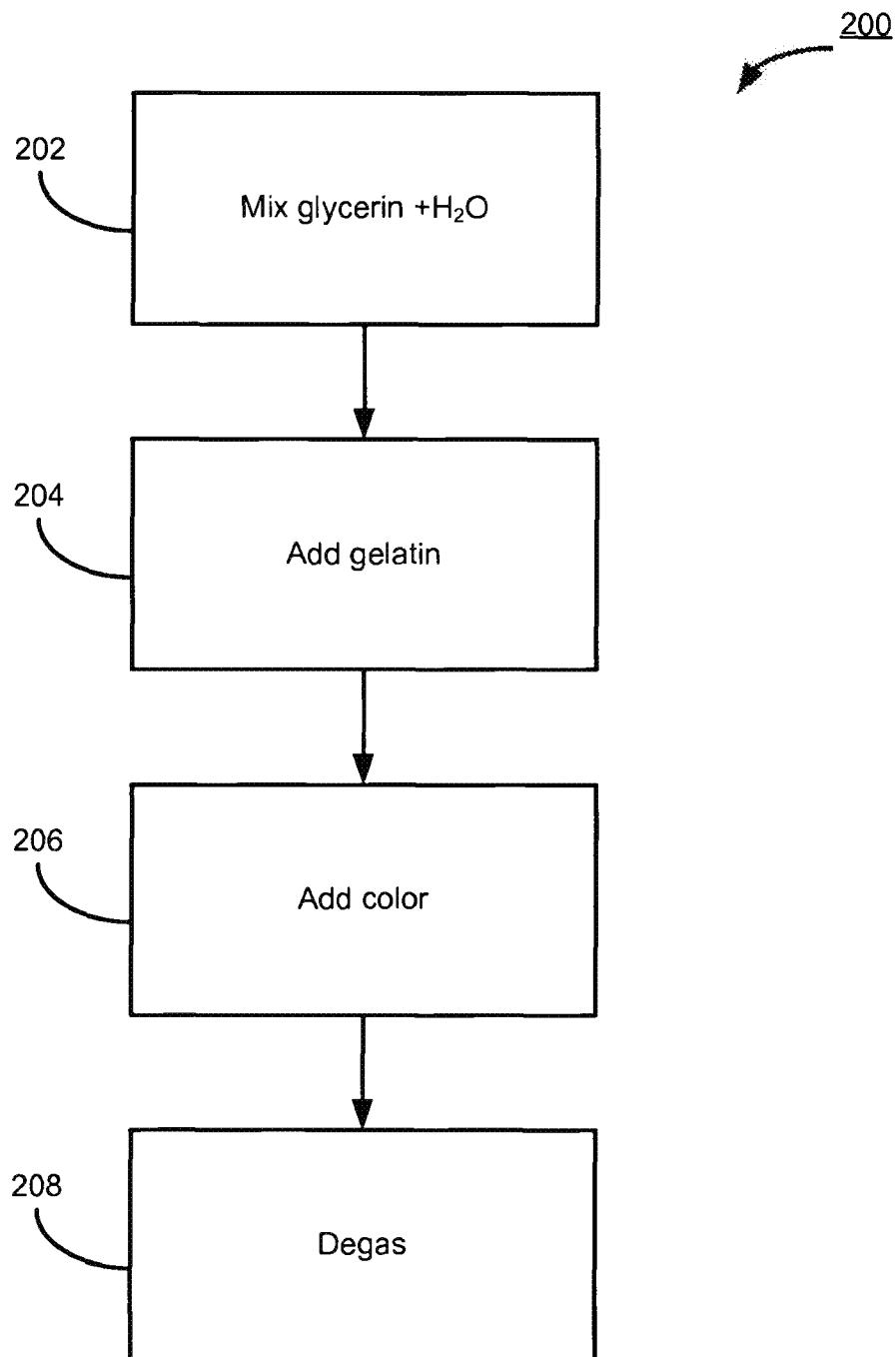


FIG. 2

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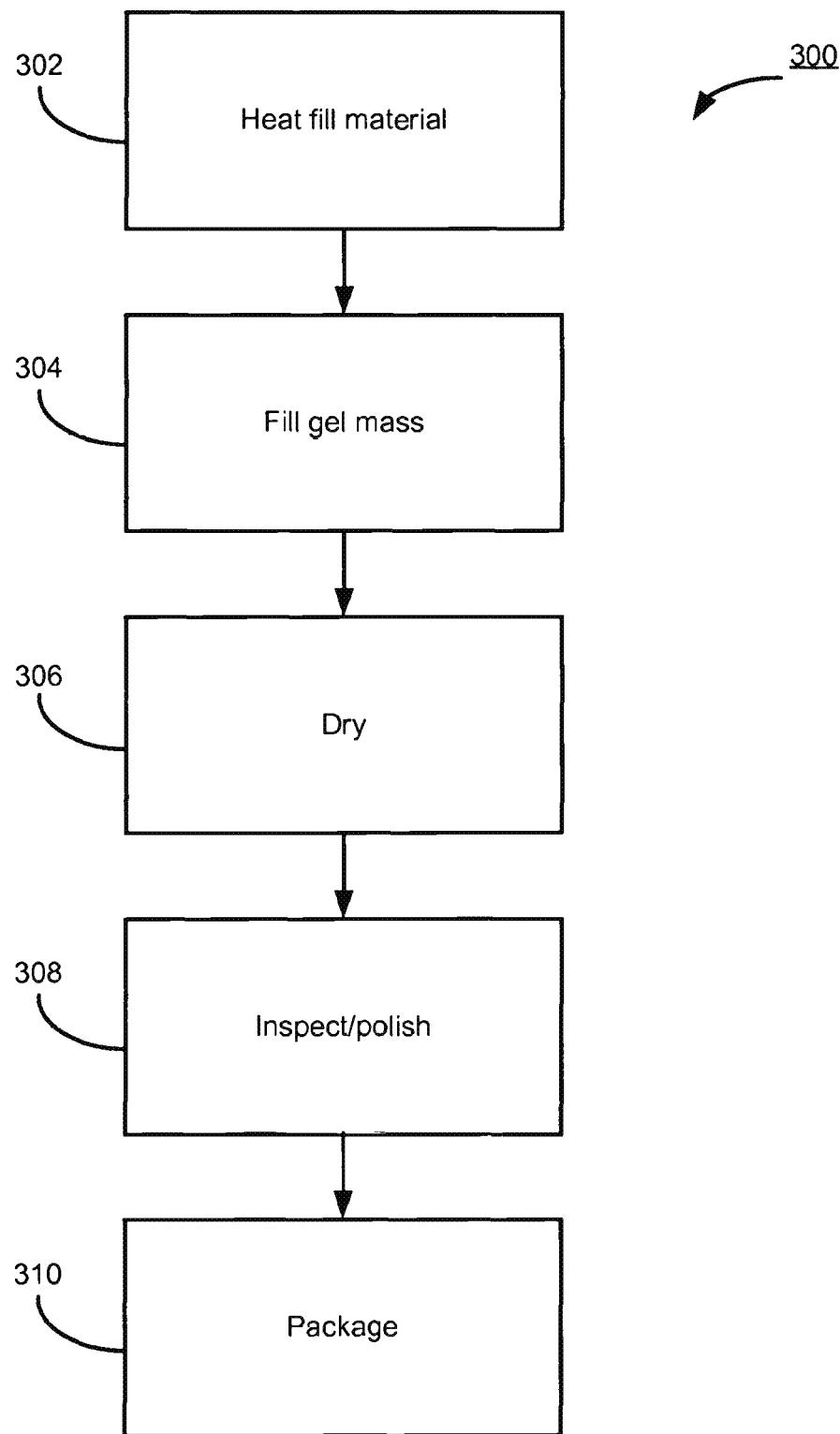


FIG. 3

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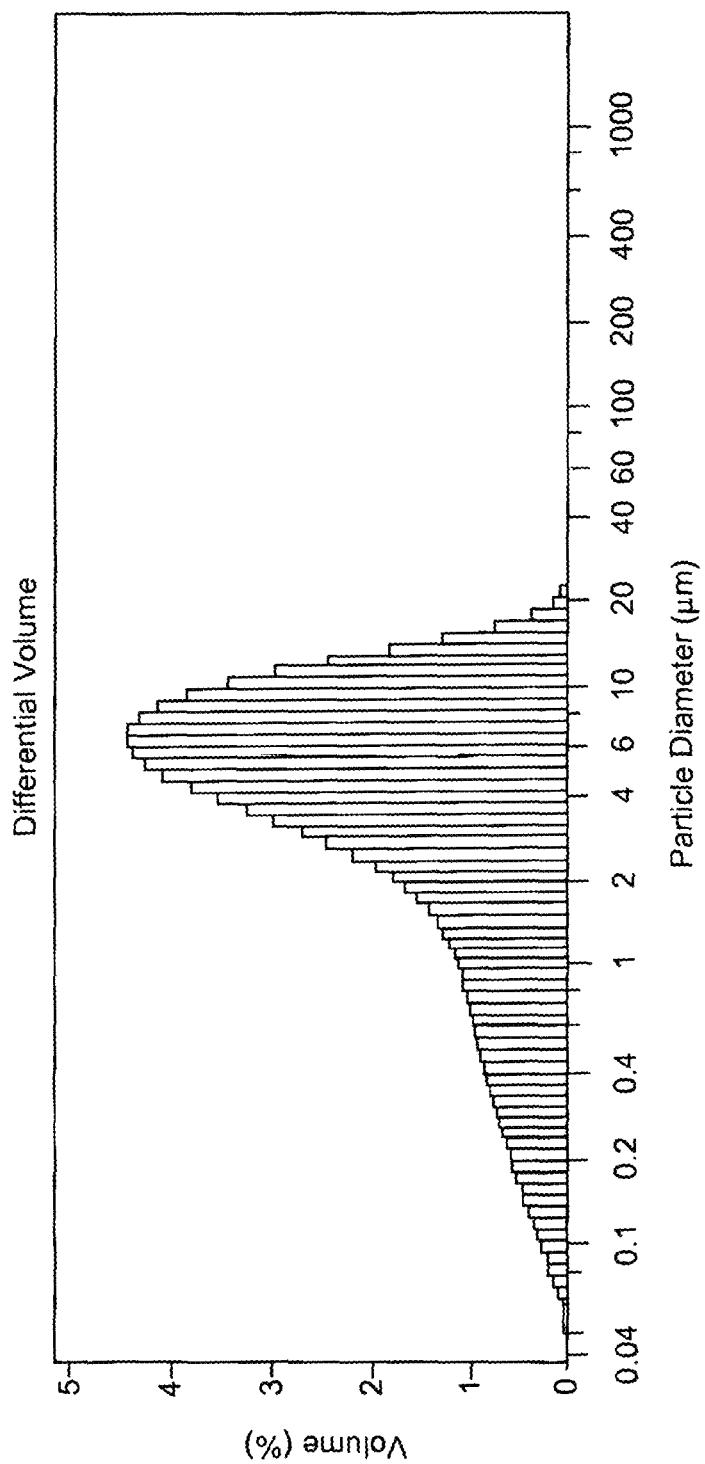


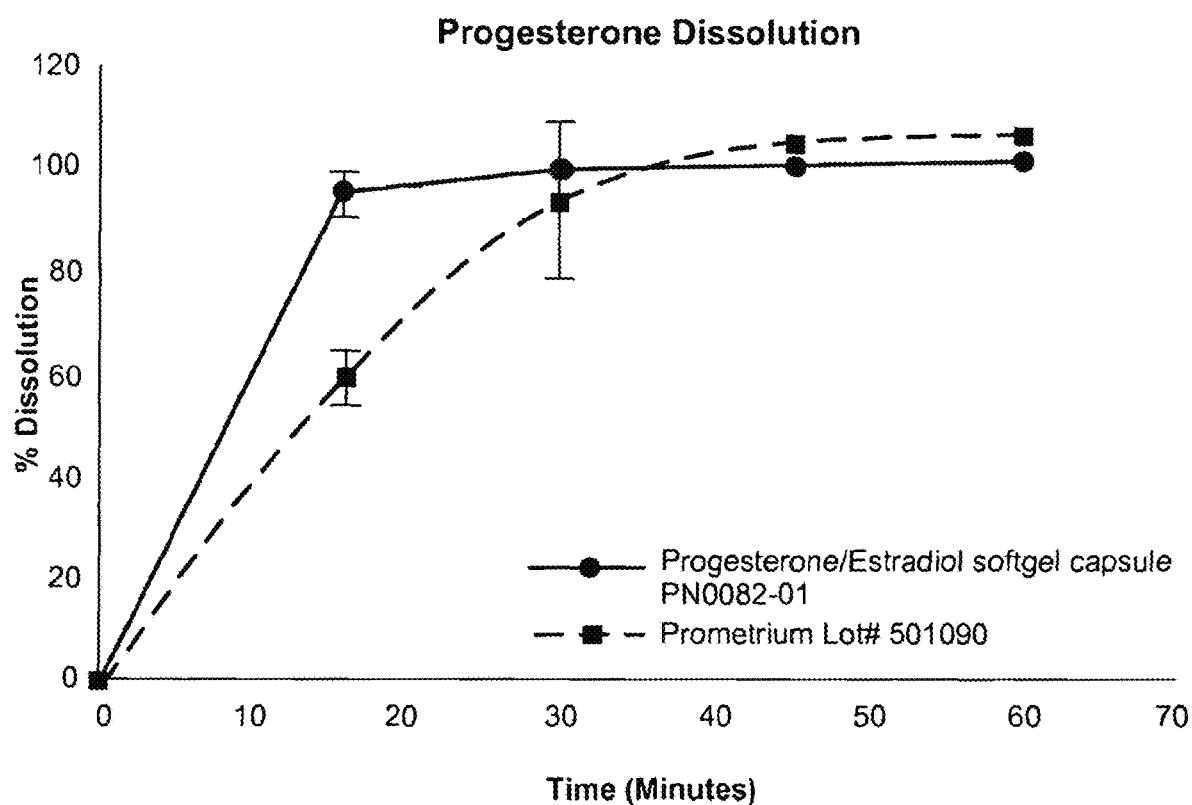
FIG. 4

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**FIG. 5**

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**NATURAL COMBINATION HORMONE
REPLACEMENT FORMULATIONS AND
THERAPIES**

**CROSS-REFERENCES TO RELATED
APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/690,955 filed Apr. 20, 2015, which is a divisional of U.S. patent application Ser. No. 14/099,582, filed Dec. 6, 2013, which is a continuation of U.S. patent application Ser. No. 13/843,428, filed Mar. 15, 2013, which is a CIP of U.S. patent application Ser. No. 13/684,002, filed Nov. 21, 2012, now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014, which claims the benefit of U.S. Provisional Patent Application No. 61/662,265, filed Jun. 20, 2012 and U.S. Provisional Patent Application No. 61/661,302 filed Jun. 18, 2012, which are incorporated herein by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, per-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequental" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly meno-pausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT."

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This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both 20 branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (Progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and 25 Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA #N019781. According to the prescribing information approved for this product (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

30 Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products 35 are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

BRIEF SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery 40 via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single 45 blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone 50 replacement therapies, each in accordance with the invention 55 are set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further

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serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein, means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein, means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “Cmax,” as used herein, refers to the maximum value of blood concentration shown on the curve that

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represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term “Tmax,” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively, AUC, Cmax and, optionally, Tmax, are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to nonactive pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil,” as used herein, may be any pharmaceutically acceptable substance, such as an organic oil, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone,” as used herein, means progesterone which is about 100% in solution, i.e., at least 98% in solution.

“Partially solubilized progesterone,” as used herein, means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micron-

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ized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg, and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	Prometrium Capsules Daily Dose		
	100 mg	200 mg	300 mg
C _{max} (ng/ml)	17.3 ± 21.9	38.1 ± 37.8	60.6 ± 72.5
T _{max} (hr)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC ₀₋₁₀ (ng × hr/ml)	43.4 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques

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established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment," or a derivative thereof, 30 contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical 40 hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 β -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially 50 useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone 55 for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone

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has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the “Beckman Device”) may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module (“ULM”). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant (“Coulter 1B”), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module (“MLM”). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, antioxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

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Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829; 10 a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul@ PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, 25 Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of 30 about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or 55 propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 60 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 50° C. In illustrative embodiments, Gelucire 44/14 is heated to about 65° C. and Capmul MCM

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is heated to about 40° C. to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides.

Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Mystic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

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High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monocaprylate, e.g., Capryol™ 90 (Gattefosse).

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65° C. in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20° C., are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40° C. or to below about 30° C., even down to room temperature.

In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glycetyl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and Labarafil® corn/apricot oil PEG-6 esters (Gattefosse).

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

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In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation, butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

Formulation A—P:50/EE:0.25:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
Capmul MCM, NF	65.49	98.24
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

Formulation B—P:50/EE:0.5:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
Capmul MCM, NF	65.32	97.98
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

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Formulation C—P:100/EE:0.5:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
Capmul MCM, NF	65.49	196.48
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

Formulation D—P:100/EE:1:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
Capmul MCM, NF	65.32	195.97
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

Formulation E—P:200/EE:2:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
Capmul MCM, NF	65.32	391.94
Gelucire 44/14, NF	1.00	6.00
Total	100.00	600.00

*Note: 1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone.

Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose

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ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

EXAMPLES

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*

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TABLE 1-continued

Ingredient	Solubility (mg/g)
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

*Literature reference—Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in Miglyol:ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labrasol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol:Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:	4	Crystallizes after 96 hours
Miglyol 812 (4:96)		
Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (70:30)		

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TABLE 3-continued

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (50:50)		
Transcutol:Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (5:80:15)		
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (50:50)		
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:65:28)		
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:47:47)		
Capmul MCM	12	Clear after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:	6	Precipitated
Capmul PG8 (75:25)		
Miglyol 812:	12	Hazy
Capmul PG8 (50:50)		
Transcutol:Miglyol 812:	12	Hazy
Capmul PG8 (5:65:28)		
Capmul MCM	12	Clear
Transcutol:Miglyol 812:	12	Hazy
Capmul PG8 (5:47:47)		
Polyethylene Glycol 400	12	clear

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Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total	100	3.25 kg	

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone,

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though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Myglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
CapmulMCM:Gelucire 44/14 (9:1)	86.4
CapmulMCM:Gelucire 44/14 (7:3)	70.5
CapmulMCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

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A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.±2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94

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TABLE 13-continued

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dis-

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persed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

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Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
				Total:	100.00 700.00 7.00

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An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65° C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

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Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, LISP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
				Total:	100.000 200.00 mg 2000.00

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The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
	Total:	100.00	600.0 mg	6000.0	

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65° C. and Capmul MCM is heated to 40° C. \pm 5° C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40° C.; the mixture is then passed through a colloid mill, e.g., three times.

Example 15

Study 352—Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bioequivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP, Micronized	0.30	2.07
Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

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Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose, and only necessary movements were allowed during this period. Thereafter, subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc., within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 0100, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. \pm 20° C. in the bio-analytical facility until analysis.

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Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters Cmax, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation				
	Geometric Mean*	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7	
AUC _{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7	
AUC _{0-∞}	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3	

*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters Cmax, AUC_{0-t} & AUC_{0-∞} were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar, but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below, for progesterone.

TABLE 19

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation				
	Geometric Mean*	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C _{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4	
AUC _{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0	
AUC _{0-∞}	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2	

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C.

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Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e., gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column), or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N₂. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The

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encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness $0.85\text{ mm}\pm0.05\text{ mm}$ using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight $\pm5\%$ (i.e., $650\pm33\text{ mg}$ and $325\pm16.3\text{ mg}$).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

Example 17

Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @ 50° C. for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if undissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had undissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50° C. , oils such as safflower oil will not be

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useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

Example 18

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1 NHCl with 3% sodium lauryl sulfate was used at 37° C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A pharmaceutical composition comprising: a fill material encapsulated in a capsule, the fill material comprising:
 - a two active pharmaceutical ingredients, the active pharmaceutical ingredients being about 1 mg of 17β -estradiol and about 100 mg of progesterone, wherein at least about 90% of the 17β -estradiol is solubilized, and wherein a first portion of the progesterone is solubilized and a second portion of the progesterone is micronized;

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- b. a solubilizing agent for the active pharmaceutical ingredients, the solubilizing agent comprising:
 - i. a medium chain oil comprising mono- and diglycerides; and
 - ii. at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides;

wherein the 17 β -estradiol and the progesterone in the capsule are present in the solubilizing agent; wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the progesterone has a solubility in the solubilizing agent of at least about 73 mg/g, and the 17 β -estradiol has a solubility in the solubilizing agent of at least about 10 mg/g; and wherein the progesterone comprises about 30% to about 35% by weight of the fill material, and the 17 β -estradiol comprises about 0.1% to about 0.4% by weight of the fill material.

2. The pharmaceutical composition of claim 1, wherein the medium chain oil comprises mono- and diglycerides of capric and caprylic acid.

3. The pharmaceutical composition of claim 1, wherein the medium chain oil comprises greater than about 75% caprylic monoglycerides and caprylic diglycerides.

4. The pharmaceutical composition of claim 1, wherein the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides comprises less than about 10% by weight of the fill material.

5. The pharmaceutical composition of claim 1, wherein the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides comprises about 1% to about 2% by weight of the fill material.

6. The pharmaceutical composition of claim 2, wherein the solubilizing agent comprises about 65 parts by weight of the medium chain oil and about one part by weight of the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides.

7. The pharmaceutical composition of claim 2, wherein the solubilizing agent comprises about 196 mg of the mono- and diglycerides of capric and caprylic acid and about 3 mg of the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides.

8. The pharmaceutical composition of claim 2, wherein the solubilizing agent consists of about 196 mg of the mono- and diglycerides of capric and caprylic acid and about 3 mg of the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides.

9. The pharmaceutical composition of claim 1, wherein the solubility of the 17 β -estradiol in the solubilizing agent is at least about 12 mg/g.

10. The pharmaceutical composition of claim 1, wherein the 17 β -estradiol is fully solubilized in the solubilizing agent.

11. The pharmaceutical composition of claim 1, wherein the 17 β -estradiol does not precipitate for at least about 14 days.

12. The pharmaceutical composition of claim 1, wherein at least about 14% by weight of the progesterone is solubilized in the solubilizing agent.

13. The pharmaceutical composition of claim 1, wherein the micronized progesterone has an X50 particle size value below about 15 microns, an X90 particle size value below about 25 microns, or both.

14. The pharmaceutical composition of claim 1, wherein the fill material has a total weight of less than about 400 mg.

15. A pharmaceutical composition comprising: a fill material encapsulated in a capsule, the fill material comprising:

- a. two active pharmaceutical ingredients, the active pharmaceutical ingredients being about 1 mg of 17 β -estradiol and about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized and a second portion of the progesterone is micronized, and the 17 β -estradiol is fully solubilized;

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diol and about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized and a second portion of the progesterone is micronized, and the 17 β -estradiol is fully solubilized;

- b. a solubilizing agent for the active pharmaceutical ingredients, the solubilizing agent comprising:

- i. a medium chain oil comprises mono- and diglycerides of capric and caprylic acid; and
- ii. at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides that is about 1% to about 2% by weight of the fill material;

wherein the 17 β -estradiol and the progesterone in the capsule are present in the solubilizing agent wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the progesterone has a solubility in the solubilizing agent of at least about 73 mg/g, and the 17 β -estradiol has a solubility in the solubilizing agent of at least about 10 mg/g; and wherein the progesterone is about 30% to about 35% by weight of the fill material, and the 17 β -estradiol is about 0.1% to about 0.4% by weight of the fill material.

16. The pharmaceutical composition of claim 15, wherein the 17 β -estradiol does not precipitate for at least about 14 days.

17. The pharmaceutical composition of claim 15, wherein the micronized progesterone has an X50 particle size value below about 15 microns, an X90 particle size value below about 25 microns, or both.

18. The pharmaceutical composition of claim 15, wherein at least about 14% by weight of the progesterone is solubilized in the solubilizing agent.

19. The pharmaceutical composition of claim 15, wherein the fill material has a total weight of less than about 400 mg.

20. A pharmaceutical composition comprising: a fill material encapsulated in a capsule, the fill material comprising:

- a. two active pharmaceutical ingredients, the active pharmaceutical ingredients being about 1 mg of 17 β -estradiol and about 100 mg of progesterone, wherein a first portion of the progesterone is solubilized and a second portion of the progesterone is micronized, and the 17 β -estradiol is fully solubilized;

- b. a solubilizing agent for the active pharmaceutical ingredients, the solubilizing agent comprising:

- i. about 196 mg of mono- and diglycerides of caprylic and capric acid; and

- ii. about 3 mg of at least one of lauroyl macrogol-32

glycerides or lauroyl polyoxyl-32 glycerides; wherein the 17 β -estradiol and the progesterone in the capsule are present in the solubilizing agent wherein the second portion of the progesterone is uniformly dispersed in the solubilizing agent; wherein the progesterone has a solubility in the solubilizing agent of at least about 73 mg/g, and the 17 β -estradiol has a solubility in the solubilizing agent of at least about 10 mg/g; and wherein the progesterone is about 30% to about 35% by weight of the fill material and the 17 β -estradiol is about 0.1% to about 0.4% by weight of the fill material.

21. The pharmaceutical composition of claim 20, wherein the 17 β -estradiol does not precipitate for at least about 14 days.

22. The pharmaceutical composition of claim 20, wherein the micronized progesterone has an X50 particle size value below about 15 microns, an X90 particle size value below about 25 microns, or both.

23. The pharmaceutical composition of claim 20, wherein at least about 14% by weight of the progesterone is solubilized in the solubilizing agent.

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- 24.** A method for manufacturing the pharmaceutical composition of claim 1, the method comprising the steps of:
- a. mixing the medium chain oil and the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides at a temperature of about 30° C. to about 50° 5
 - C. until the at least one of lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides is dissolved in the medium chain oil to form a first mixture;
 - b. adding 17 β -estradiol to the first mixture to form a second mixture; 10
 - c. adding micronized progesterone to the second mixture to form a fill material;
 - d. encapsulating the fill material in a capsule.

25. The method of claim 24, wherein the mixing the medium chain oil and the at least one of lauroyl macrogol-32 15 glycerides or lauroyl polyoxyl-32 glycerides takes place at a temperature of about 40° C. \pm 5° C.

26. The method of claim 24, wherein the medium chain oil comprises mono- and diglycerides of capric and caprylic acid. 20

27. The method of claim 24, wherein the fill material has a total weight of less than about 400 mg.

28. The pharmaceutical composition of claim 1, wherein up to about 14% by weight of the progesterone is solubilized in the solubilizing agent. 25

29. The pharmaceutical composition of claim 15, wherein up to about 14% by weight of the progesterone is solubilized in the solubilizing agent.

30. The pharmaceutical composition of claim 20, wherein up to about 14% by weight of the progesterone is solubilized 30 in the solubilizing agent.

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