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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

THERAPEUTICSMD, INC., Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LIMITED, Defendants.	Civil Action No. _____ (Filed Electronically)

COMPLAINT

Plaintiff TherapeuticsMD, Inc. ("TherapeuticsMD" or "Plaintiff"), by its undersigned attorneys, for its Complaint against defendants Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Limited ("Teva Ltd.") (collectively, "Teva" or "Defendants"), alleges:

NATURE OF THE ACTION

1. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code, involving U.S. Patent No. 10,888,516 ("the '516 patent" or "patent-in-suit") (attached as Exhibit A).

THE PARTIES

2. TherapeuticsMD, Inc. 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 33487.

3. TherapeuticsMD, Inc. is the owner of New Drug Application ("NDA") No. 208564, which was approved by the U.S. Food and Drug Administration ("FDA") for the manufacture and sale of Imvexxy® (estradiol vaginal inserts) 4 mcg and 10 mcg.

4. TherapeuticsMD, Inc. is the current owner and assignee of each of the eleven (11) patents listed in FDA's publication titled, "Approved Drug Products with Therapeutics Equivalence Evaluations" (commonly known as the "Orange Book") as covering TherapeuticsMD's Imvexxy®, of which one (1) is the patent-in-suit.

5. Upon information and belief, defendant Teva Ltd. is a corporation organized and existing under the laws of Israel, having a principal place of business at 124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel.

6. Upon information and belief, Teva Ltd. represented in its SEC filings that it is the "leading generic pharmaceutical company in the United States" and, in 2020, it "led the U.S. generics market in total prescriptions and new prescriptions." Teva Ltd.'s Form 10-K for the fiscal year ending in December 31, 2020, at 3, 56.

7. Upon information and belief, Teva Ltd. operates through a global network of subsidiaries that it directly or indirectly owns and controls, including defendant Teva USA. In

its most recent SEC form 10-K, Teva Ltd. stated that it "operate[s] [its] business through three segments: North America, Europe and International Markets." *Id*. at 2. In particular, Teva Ltd. stated that "Anda, [its] distribution business in the United States, distributes generic, specialty and [over the counter] pharmaceutical products from various third party manufacturers to independent retail pharmacies, pharmacy retail chains, hospitals and physician offices in the United States." *Id.* at 3.

8. As of December 31, 2020, Teva Ltd.'s "generic products pipeline" included "213 product applications awaiting FDA approval" where "70% of [these] pending applications include a paragraph IV patent challenge." *Id.* at 58. Upon information and belief, Teva Ltd.'s "generic products pipeline" includes the generic pharmaceutical products for which Teva USA is the named Abbreviated New Drug Application ("ANDA") applicant.

9. Upon information and belief, Teva Ltd. is in the business of, among other things: (i) the development and manufacture of generic pharmaceutical products for sale throughout the world, including throughout the United States and, more specifically, throughout the State of New Jersey; (ii) in concert with and/or through its various subsidiaries, including defendant Teva USA, the preparation, submission, and filing of Abbreviated New Drug Applications ("ANDAs") seeking FDA approval to market generic drugs throughout the United States, including throughout the State of New Jersey; and (iii) in concert with and/or through its various subsidiaries, including defendant Teva USA, the distribution of generic pharmaceutical products for sale throughout the United States, including throughout the State of New Jersey.

10. Upon information and belief, defendant Teva USA is a corporation organized and existing under the laws of the State of Delaware having principal places of business located at

400 Interpace Parkway, Parsippany, New Jersey 07054 and 1090 Horsham Road, North Wales, Pennsylvania 19454.

11. Upon information and belief, Teva USA is a wholly owned subsidiary of Teva Ltd. Upon information and belief, Teva USA acts at the direction of, under the control of, and for the benefit of Teva Ltd., and is controlled and/or dominated by Teva Ltd. Upon information and belief, Teva USA and Teva Ltd. have at least one officer and/or director in common.

12. Upon information and belief, Teva USA is in the business of, among other things: (i) the development and manufacture of generic pharmaceutical products for sale throughout the United States, including throughout the State of New Jersey; (ii) alone or in concert with and/or through its parent and various subsidiaries, including defendant Teva Ltd., the preparation, submission, and filing of ANDAs seeking FDA approval to market generic drugs throughout the United States, including throughout the State of New Jersey; and (iii) alone or in concert with and/or through its parent and various subsidiaries, including defendant Teva Ltd., the distribution of generic pharmaceutical products for sale throughout the United States, including throughout the State of New Jersey.

13. Upon information and belief, Defendants or their affiliates manufacture and/or direct the manufacture of generic pharmaceutical products for which Teva USA is the named ANDA applicant. Upon information and belief, Defendants each, directly or indirectly, derive substantial revenue from the sales of such generic pharmaceutical products.

JURISDICTION AND VENUE

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

15. This Court has personal jurisdiction over Defendants under: (i) Fed. R. Civ. P. 4(k)(1); (ii) Fed. R. Civ. P. 4(k)(2); and (iii) N.J. Ct. R. 4:4-4.

16. Teva USA has already consented to personal jurisdiction and venue in four related matters: *TherapeuticsMD, Inc. v. Teva Pharmaceuticals USA, Inc.*, C.A. No. 20-3485 (BRM)(ESK), in its Answer filed on June 15, 2020 and Amended Answer filed on July 2, 2020 (*see* 20-3485 (BRM)(ESK), ECF Nos. 10, 20); *TherapeuticsMD, Inc. v. Teva Pharmaceuticals USA, Inc.*, C.A. No. 20-8809 (BRM)(ESK), in its Answer filed on August 5, 2020 (*see* 20-8809 (BRM) (ESK), ECF. No. 12); *TherapeuticsMD, Inc. v. Teva Pharmaceuticals USA, Inc.*, C.A. No. 20-11087 (BRM)(ESK), in its Answer filed on September 9, 2020 (*see* 20-11087 (BRM)(ESK), ECF No. 11); and *TherapeuticsMD, Inc. v. Teva Pharmaceuticals USA, Inc.*, C.A. No. 20-17496 (BRM)(ESK), in its Answer filed on December 21, 2020 (*see* 20-17496, ECF No. 14).

17. This Court has personal jurisdiction over Teva USA at least because, upon information and belief: (i) Teva USA maintains a principal place of business in New Jersey located at 400 Interpace Parkway, Parsippany, New Jersey 07054; (ii) Teva USA is doing business in New Jersey and maintains continuous and systematic contacts with this Judicial District; (iii) Teva USA, together with its parent Teva Ltd., is in the business of developing and manufacturing generic pharmaceutical products for importation, sale, and/or distribution in the State of New Jersey; (iv) Teva USA, together with its parent Teva Ltd., has committed, induced, and/or contributed to acts of patent infringement in New Jersey; (v) Teva USA has previously submitted to the jurisdiction of this Court, has availed itself of New Jersey's legal protections in hundreds of prior litigations, and previously consented to personal jurisdiction and venue in this Judicial District[1]; and (vi) Teva USA's May 13, 2021 notice of paragraph IV certification

[1] This Court has personal jurisdiction over Teva Ltd. and Teva USA because Teva Ltd. and Teva USA have previously submitted to the jurisdiction of this Court and have further previously availed themselves of this Court by initiating lawsuits, consenting to this Court's jurisdiction,

("Notice Letter") identified the correspondence address for Teva USA's offer of confidential access as 400 Interpace Parkway, Parsippany, NJ 07054.

18. Upon information and belief, Teva USA is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey with Business Identification Number 0100250184. Upon information and belief, Teva USA is registered with the State of New Jersey's Department of Health as a drug & medical device "manufacturer and wholesaler" and "wholesaler" with Registration Numbers 5000583 and 5003436, respectively.

19. In its Notice Letter, Teva USA asserts that it prepared, submitted, and filed with FDA, pursuant to § 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (codified at 21 U.S.C. § 355(j)), ANDA No. 214137, seeking approval to engage in the commercial manufacture, use, and/or sale of Estradiol Vaginal Insert 4 mcg and 10 mcg ("Defendants' ANDA Product") before the expiration of the '516 patent throughout the United States, including in this Judicial District.

20. This Court has personal jurisdiction over Defendants at least because, upon information and belief, if ANDA No. 214137 receives final approval, Defendants' ANDA

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and asserting counterclaims in other civil actions initiated in this jurisdiction. *See, e.g.*, *Teva Pharmaceuticals USA, Inc., et al. v. Sandoz Inc., et al.*, No. 3-17-cv-00275 (FLW)(DEA) (D.N.J.) (Teva USA and Teva Ltd. filed complaint for patent infringement); *Teva Pharmaceuticals USA, Inc., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, No. 3-17-cv-00517 (FLW)(DEA) (D.N.J.) (same); *Teva Pharmaceuticals USA, Inc., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, No. 2-15-cv-00471 (CCC)(MF) (D.N.J.) (same); *Teva Pharmaceuticals USA, Inc., et al. v. Synthon Pharmaceuticals, Inc., et al.*, No. 2-15-cv-00472 (CCC)(MF) (D.N.J.) (same); *Adapt Pharma Operations Ltd., et al. v. Teva Pharmaceuticals USA, Inc., et al.*, No. 2-18-cv-09880 (JLL)(JAD) (D.N.J) (Teva USA and Teva Ltd. did not contest jurisdiction); *Janssen Pharmaceuticals, Inc., et al. v. Teva Pharmaceuticals USA, Inc., et al.*, No. 2-18-cv-00734 (CCC)(MF) (D.N.J.) (same); *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Teva Pharmaceuticals USA, Inc., et al.*, No. 3-17-cv-11510 (MAS)(LHG) (D.N.J.) (Teva USA and Teva Ltd. filed counterclaims and did not contest jurisdiction).

Product will be manufactured, sold, distributed, and/or used by Defendants in New Jersey, prescribed by physicians practicing in New Jersey, and/or administered to patients in New Jersey.

21. Upon information and belief, Teva USA's acts of preparing and filing ANDA No. 214137 and directing notice of its ANDA submission to Plaintiff were performed at the direction of, with the authorization of, and with the cooperation, participation, assistance, and, at least in part, the benefit of Teva Ltd. These are acts with real and injurious consequences giving rise to this infringement action, including the present and/or anticipated commercial manufacture, use, and/or sale of Defendants' ANDA Product before the expiration of the '516 patent throughout the United States, including in this Judicial District. Because defending against an infringement lawsuit such as this one is an essential and expected part of a generic ANDA filer's business, Teva Ltd. and Teva USA reasonably anticipate being sued in New Jersey.

22. This Court has personal jurisdiction over Teva Ltd. because, among other things: (a) Teva Ltd. has purposefully directed its activities and the activities of Teva USA, its wholly owned subsidiary, at residents and corporate entities within the State of New Jersey; (b) the claims set forth herein as to Teva Ltd. arise out of or relate to those activities; (c) Teva Ltd.'s contacts with the State of New Jersey (direct and/or indirect) are continuous and systematic; and (d) it is reasonable and fair for this Court to exercise personal jurisdiction over Teva Ltd.

23. Venue is proper in this Court under 28 U.S.C. §§ 1391(b), 1391(c), and/or 1400(b).

FACTS COMMON TO ALL COUNTS

24. TherapeuticsMD's Imvexxy® is sold and marketed under NDA No. 208564, which was approved by FDA as a New Product on May 29, 2018.

25. Because TherapeuticsMD conducted efficacy clinical trials to secure FDA approval of Imvexxy®, FDA granted Imvexxy® three years of regulatory exclusivity.

26. Imvexxy® is supplied as a vaginal insert with either 4 mcg or 10 mcg of estradiol. Estradiol, the active ingredient in Imvexxy®, is an estrogen that is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

27. NDA No. 208564 pertains to Imvexxy® 4 mcg and 10 mcg.

28. Imvexxy®'s recommended dosage is one vaginal insert daily for two weeks, followed by one insert twice weekly.

29. FDA's Orange Book lists eleven (11) patents as covering TherapeuticsMD's Imvexxy®. Pursuant to 21 U.S.C. §§ 355(b)(1) and 355(c)(2), these eleven (11) patents were submitted to FDA with or after the approval of NDA No. 208564. These eleven (11) patents are listed in the Orange Book as covering Imvexxy®.

30. Teva USA sent Teva's Notice Letters to TherapeuticsMD, purportedly pursuant to § 505(j)(2)(A)(iv) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(iv), and § 314.95 of Title 21 of the Code of Federal Regulations, regarding ANDA No. 214137. In these letters, Teva USA states that Teva USA's ANDA has been submitted under § 505(j) of the FDCA, with paragraph IV certifications to obtain approval to engage in the commercial manufacture, use, or sale of Estradiol Vaginal Insert 4 mcg and 10 mcg, before the expiration of United States Patent Nos. 9,180,091; 9,289,382; 10,258,630; 10,398,708; 10,471,072; 10,537,581; 10,568,891; 10,668,082; 10,806,697; and 10,835,487. United States Patent Nos. 9,180,091; 9,289,382; 10,258,630; 10,398,708; 10,471,072; 10,537,581; 10,568,891; 10,668,082; 10,806,697; and 10,835,487 are ten (10) of the eleven (11) patents listed in FDA's Orange Book as covering Imvexxy®.

31. TherapeuticsMD filed a complaint against Teva USA and Teva Ltd. in this Court on April 1, 2020 alleging infringement of United States Patent Nos. 9,180,091; 9,289,382; 10,258,630; 10,398,708; 10,471,072. *TherapeuticsMD, Inc. v. Teva USA, Inc.*, C.A. No. 20-3485 (BRM)(ESK), ECF No. 1. TherapeuticsMD filed a second complaint against Teva USA and Teva Ltd. in this Court on July 13, 2020 alleging infringement of United States Patent Nos. 10,537,581 and 10,568,891. *TherapeuticsMD, Inc. v. Teva USA, Inc.*, C.A. No. 20-8809 (BRM)(ESK), ECF No. 1. TherapeuticsMD filed a third complaint against Teva USA and Teva Ltd. in this Court on August 21, 2020 alleging infringement of United States Patent No. 10,668,082. TherapeuticsMD filed a fourth complaint against Teva USA and Teva Ltd. in this Court on November 30, 2020 alleging infringement of United States Patent Nos. 10,806,697 and 10,835,487. *TherapeuticsMD, Inc. v. Teva USA, Inc.*, C.A. No. 20-17496 (BRM)(ESK), ECF No. 1. These four actions have been consolidated for all purposes, including trial, under Civil Action No. 20-3485 (consolidated). *TherapeuticsMD, Inc. v. Teva USA, Inc.*, C.A. No. 20-3485 (BRM)(ESK) (consolidated), ECF No. 51.

32. Teva USA sent a letter to TherapeuticsMD dated May 13, 2021, purportedly pursuant to § 505(j)(2)(A)(iv) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(iv), and § 314.95 of Title 21 of the Code of Federal Regulations, regarding ANDA No. 214137 (the "Notice Letter").

33. The Notice Letter states that Teva USA's ANDA has been submitted under § 505(j) of the FDCA, with a paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of Estradiol Vaginal Insert 4 mcg and 10 mcg, before the expiration of the '516 patent. The '516 patent is one (1) of the eleven (11) patents listed in FDA's Orange Book as covering Imvexxy®.

34. Upon information and belief, Teva USA's ANDA was submitted under § 505(j)(2) of the FDCA with a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the '516 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Defendants' ANDA Product.

35. Upon information and belief, the proposed prescribing information for Defendants' ANDA Product includes a header titled, "Indications and Usage," and states that Defendants' ANDA Product is for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

36. Upon information and belief, the proposed prescribing information for Defendants' ANDA Product includes a header titled, "Dosage and Administration," and states that Defendants' ANDA Product should be administered intravaginally; insert with the smaller end up for a depth of about two inches into the vaginal canal. Insert 1 daily at approximately the same time for 2 weeks, followed by 1 insert twice weekly, every three to four days (for example, Monday and Thursday). Generally, women should be started at the 4 mcg dosage strength. Dosage adjustment should be guided by the clinical response.

37. Upon information and belief, administration of Defendants' ANDA Product will be indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

38. The '516 patent, titled, "Soluble Estradiol Capsule For Vaginal Insertion," was duly and legally issued by the U.S. Patent and Trademark Office on January 12, 2021, to TherapeuticsMD, Inc. on assignment from the inventors.

39. Pursuant to 21 U.S.C. § 355(b)(1), the '516 patent was submitted to FDA after the approval of NDA No. 208564. The '516 patent was subsequently listed in the Orange Book as covering Imvexxy®.

40. The Notice Letter does not include any unenforceability contentions with respect to any claims of the patent-in-suit.

FIRST COUNT
(Defendants' Infringement of the '516 patent)

41. TherapeuticsMD repeats and re-alleges each of the foregoing paragraphs as if fully set forth herein.

42. Upon information and belief, Teva USA, purportedly at the direction and control of Teva Ltd., prepared ANDA No. 214137.

43. Upon information and belief, Teva Ltd. provided material and significant support to Teva USA in the preparation of ANDA No. 214137.

44. Upon information and belief, Teva USA, purportedly at the direction and control of Teva Ltd., submitted ANDA No. 214137 to FDA pursuant to § 505(j) of the FDCA (codified at 21 U.S.C. § 355(j)) for the purpose of seeking FDA approval to market Defendants' ANDA Product prior to the expiration of the patent-in-suit.

45. Upon information and belief, ANDA No. 214137 is based upon Imvexxy® (estradiol vaginal inserts), 4 mcg and 10 mcg, as its reference listed drug.

46. Upon information and belief, Defendants' ANDA Product is Estradiol Vaginal Insert, 4 mcg and 10 mcg.

47. Upon information and belief, Teva USA, purportedly at the direction and control of Teva Ltd., submitted ANDA No. 214137 with a paragraph IV certification to the '516 patent for the purpose of obtaining FDA approval to engage in the commercial manufacture, use,

offering for sale, sale, and/or importation of Defendants' ANDA Product before the expiration of the '516 patent.

48. Under 21 U.S.C. § 355(j)(2)(B), the filer of an ANDA containing a paragraph IV certification must provide notice of the filing to each patent owner and each NDA holder. Under 21 U.S.C. § 355(j)(2)(B)(iv)(II), such notice must "include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed." Likewise, 21 C.F.R. § 314.95(c)(7) requires that such notice include a "detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement must include: "For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "[f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the ground supporting the allegation." 21 C.F.R. § 314.95(c)(7)(i)–(ii).

49. Upon information and belief, as of the date of Notice Letter, Teva USA and Teva Ltd. were aware of the statutory provisions and regulations set out in 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(7).

50. Purportedly in accordance with 21 U.S.C. § 355(j)(2)(B)(iv) and 21 C.F.R. § 314.95(d)(1), Teva USA sent a copy of the Notice Letter to TherapeuticsMD, Inc. at 951 Yamato Road, Suite 220, Boca Raton, Florida 33431.

51. Under 35 U.S.C. § 271(e)(2)(A), Teva USA's submission, at the direction and control of Teva Ltd., of ANDA No. 214137 with a paragraph IV certification to the '516 patent for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of Defendants' ANDA Product before the expiration of the '516 patent is an act of infringement of the '516 patent.

52. Upon information and belief, Teva USA and Teva Ltd. will commercially manufacture, use, offer to sell, and/or sell within the United States, and/or import into the United States, Defendants' ANDA Product if ANDA No. 214137 ever receives final FDA approval.

53. Upon information and belief, Teva USA and Teva Ltd.'s commercial manufacture, use, offering to sell, and/or sale within the United States, and/or importation into the United States, of Defendants' ANDA Product would infringe, directly and/or indirectly, one or more of the '516 patent's claims under 35 U.S.C. § 271.

54. Upon information and belief, Teva USA and Teva Ltd.'s commercial offering for sale and/or sale of Defendants' ANDA Product will induce and/or contribute to third-party infringement of one or more claims of the '516 patent under 35 U.S.C. § 271.

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

56. The acts of infringement set forth above will cause TherapeuticsMD irreparable harm for which there is no adequate remedy at law, unless Teva USA and Teva Ltd. are preliminarily and permanently enjoined by this Court.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests the following relief:

A. A judgment declaring that the '516 patent is valid and enforceable;

B. A judgment, pursuant to 35 U.S.C. § 271(e)(2)(A), declaring that Defendants infringed the '516 patent by submitting to FDA ANDA No. 214137 with a paragraph IV certification for the purpose of obtaining approval for the commercial manufacture, use, or sale of Defendants' ANDA Product before the expiration of the '516 patent;

C. A judgment, pursuant to 35 U.S.C. § 271(a), (b), and/or (c), declaring that the commercial manufacture, use, offering to sell, or sale within the United States, and/or

importation into the United States, of Defendants' ANDA Product before the expiration of the '516 patent (including any regulatory extension) would directly and/or indirectly infringe the '516 patent;

D. An order, pursuant to 35 U.S.C. § 271(e)(4)(A), § 281, and § 283, that the effective date of any final approval of ANDA No. 214137 shall be no earlier than the date on which the '516 patent expires (including any regulatory extension);

E. An order, pursuant to 35 U.S.C. § 271(e)(4)(B), § 281, and § 283, preliminarily and permanently enjoining Defendants, their officers, agents, servants, employees, attorneys, and any person in active concert or participation or privity with Defendants, from engaging in the commercial manufacture, use, offering to sell, or sale within the United States, and/or importation into the United States, of Defendants' ANDA Product until the expiration of the '516 patent (including any regulatory extension);

F. A judgment, pursuant to 35 U.S.C. § 271(e)(4)(C) and § 284, awarding TherapeuticsMD damages or other monetary relief if Defendants commercially manufacture, use, offer to sell, or sell within the United States, and/or import into the United States, any product that is the subject of ANDA No. 214137, prior to the expiration of the '516 patent (including any regulatory extension);

G. A judgment, pursuant to 35 U.S.C. § 271(e)(4)(C) and § 284, declaring that Defendants' infringement of the '516 patent is willful and awarding TherapeuticsMD enhanced damages if Defendants commercially manufacture, use, offer to sell, or sell within the United States, and/or import into the United States, any product that is the subject of ANDA No. 214137, prior to the expiration of the '516 patent (including any regulatory extension);

H. A judgment, pursuant to 35 U.S.C. § 285, declaring that this is an exceptional case and awarding TherapeuticsMD its attorneys' fees and costs; and

I. Such other and further relief as this Court may deem just and proper.

Dated: June 21, 2021

By: s/ William C. Baton

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *TherapeuticsMD, Inc. v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 20-3485 (BRM)(ESK) (D.N.J.) (consolidated) is related to the matter in controversy because the matter in controversy involves the same plaintiff, one of the same defendants, and because Teva USA is seeking FDA approval to market generic versions of the same pharmaceutical product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: June 21, 2021

By: s/ William C. Baton

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Exhibit A

US010888516B2

(12) United States Patent

Bernick et al.

(10) Patent No.: US 10,888,516 B2
(45) Date of Patent: *Jan. 12, 2021

(54) **SOLUBLE ESTRADIOL CAPSULE FOR VAGINAL INSERTION**

(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); **Thorsteinn Thorsteinsson**, Boynton Beach, FL (US); **Janice Louise Cacace**, St. Petersburg, FL (US); **Frederick D. Sancilio**, Stuart, FL (US); **Neda Irani**, 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.

(21) Appl. No.: **16/833,213**

(22) Filed: **Mar. 27, 2020**

(65) **Prior Publication Data**

US 2020/0289529 A1 Sep. 17, 2020

Related U.S. Application Data

(63) Continuation of application No. 14/649,818, filed as application No. PCT/US2013/046443 on Jun. 18, 2013, now abandoned.

(60) Provisional application No. 61/745,313, filed on Dec. 21, 2012.

(51) **Int. Cl.**

A61K 9/00	(2006.01)
A61K 31/565	(2006.01)
A61K 9/02	(2006.01)
A61K 9/107	(2006.01)
A61K 9/48	(2006.01)
A61K 31/57	(2006.01)
A61K 47/10	(2017.01)
A61K 47/14	(2017.01)
A61K 47/44	(2017.01)

(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)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

According to various embodiments of this disclosure, pharmaceutical formulations comprising solubilized estradiol are provided. In various embodiments, such formulations are encapsulated in soft capsules which may be vaginally inserted for the treatment of vulvovaginal atrophy.

19 Claims, 2 Drawing Sheets

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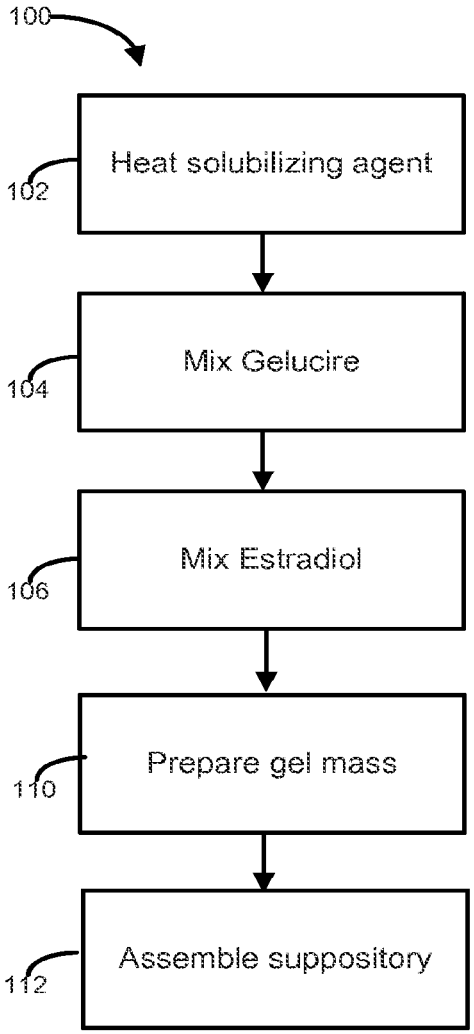
100
Heat solubilizing agent
102
Mix Gelucire
104
Mix Estradiol
106
Prepare gel mass
110
Assemble suppository
112

Fig. 1

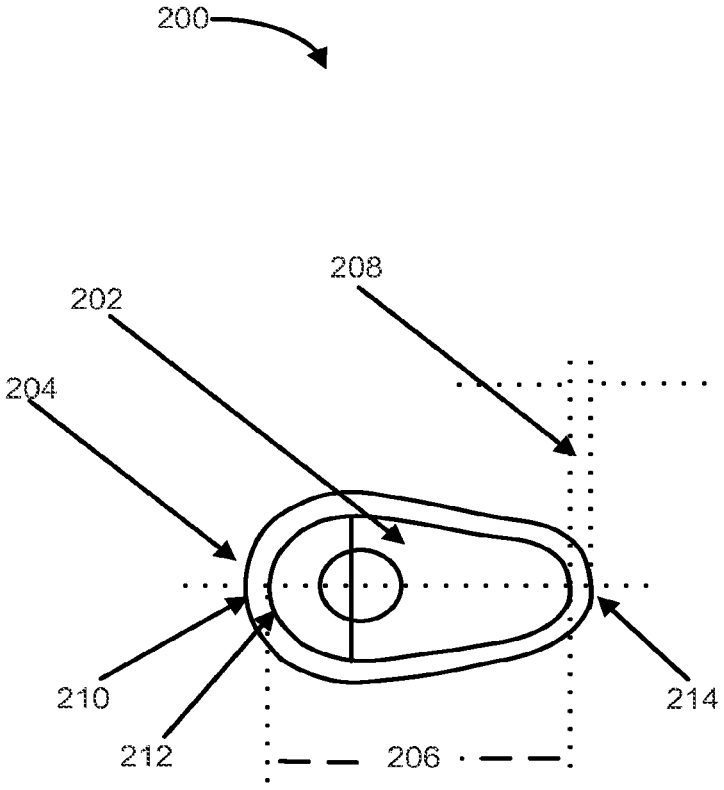

Fig. 2

SOLUBLE ESTRADIOL CAPSULE FOR VAGINAL INSERTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application 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. Provisional Application Ser. No. 61/745,313, entitled "SOLUBLE ESTRADIOL CAPSULE FOR VAGINAL INSERTION," which was filed on Dec. 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. 13/843,428, 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.

BACKGROUND

Field

Postmenopausal women frequently suffer from certain vaginally localized states including, for example, atrophic vaginitis or vulvar and vaginal atrophy (hereinafter "vulvovaginal atrophy" or "WA") with symptoms including, for example, dryness, itching, soreness, irritation, bleeding and dyspareunia; with urinary frequency, urgency, urinary discomfort and incontinence also occurring (singularly and collectively, "estrogen-deficient urinary state(s)"). For the sake of clarity, the terms "atrophic vaginitis" and vulvovaginal atrophy are used herein interchangeably. The molecular morphology of WA is well known in the medical field.

Each of these VVA-related states, inter alia, are symptoms associated with decreased estrogenization of the vulvovaginal tissue, and can even occur in women treated with oral administration of an estrogen-based pharmaceutical drug product. Although WA is most common with menopausal women, it can occur at any time in a woman's life cycle.

WA-related states are generally treated with local administration of an estrogen-based natural or synthetic hormone in the form of a topically applied gel or cream, or through vaginal insertion of a compressed tablet. These forms of administration can provide low levels of circulating estrogen but are not intended to contribute to the treatment of other states related to estrogen deficiencies typically treated via administration of a systemically absorbed estrogen product. For example, such systemically absorbed products include orally administered formulations as well as creams, gels, sprays, and transdermally delivered products. However, vaginal gels and creams may rub, wear or wash off before the estrogen is fully absorbed into the local tissue. In addition, various commercially available estrogen-containing creams contain an alcohol such as benzyl alcohol and/or stearyl alcohol. The use of such products may result in itching or burning when applied. The above referenced vaginal creams and gels require insertion via a reusable vaginal applicator/plunger for which patients complain of difficulty to accurately dose, discomfort or pain upon insertion, and increased trauma to the genital mucosa all in relation to the vaginal applicator. Furthermore, the reusable applicator/plunger is also difficult to clean resulting in hygienic concerns as well as increased rates of infection all decreasing the ongoing compliance of the therapy.

Similarly, vaginal suppositories in the form of inserted tablets may not fully dissolve, reducing the effective dose of absorbed estrogen; may cause unwanted and unnecessary vaginal discharge; may cause an increase of vulvovaginal pruritus and/or back pain; and the insertion, itself, using the applicator provided with the reference-listed tableted drug, Vagifem® (Novo Nordisk; Princeton, N.J.), may cause a rupture of the vaginal fornix.

There has been at least one attempt at providing a soluble or suspended estrogen capsule for vaginal insertion as described in U.S. Pat. No. 6,060,077 (the '077 patent). The '077 patent provides for a non-systemic treatment for vaginal dryness in menopausal women using an immediate or slow-release formulation comprising a natural estrogen compound in solution or suspension in a lipophilic agent, a hydrophilic gel-forming bioadhesive agent, a gelling agent for the lipophilic agent, and a hydrodispersible agent in a hard or soft capsule. It is specifically stated that these formulations are designed to avoid systemic passage of estradiol following administration. Once in contact with vaginal secretions, these formulations require the presence of the hydrophilic gel-forming bioadhesive agent to react with the hydrodispersible agent to form an estrogen-containing emulsion to facilitate absorption. A practical issue arises when attempting to use this medicament when vaginal secretions are required to activate the formulation while the treatment is designed to treat vaginal dryness.

Accordingly, an estrogen-based vaginal suppository that provides an ease of administration/insertion, improved safety of insertion, lacking or minimizing vaginal discharge following administration, and that does not require vaginal secretions to activate the formulation could provide a more effective dosage form with improved efficacy, safety and patient compliance.

SUMMARY

According to various embodiments of this disclosure, encapsulated pharmaceutical formulations comprising solubilized estradiol are provided. Such formulations are encapsulated in soft capsules which are vaginally inserted for the treatment of vulvovaginal atrophy.

BRIEF DESCRIPTION OF THE DRAWINGS

The subject matter of the present invention is particularly pointed out and distinctly claimed below. A more complete understanding of the present invention, however, may best be obtained by referring to the detailed description and claims when considered in connection with the figures, wherein like numerals denote like elements and wherein:

FIG. **1** is a flow diagram illustrating a process in accordance with various embodiments of the invention; and

FIG. **2** illustrates a suppository in accordance with various embodiments of the invention.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Definitions

The term "active pharmaceutical ingredient" as used herein, means the active compound(s) used in formulating a drug product.

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of an active pharmaceutical ingredient (e.g., estradiol, which is also referred to in the literature as 17β-estradiol, oestradiol, or E2) over time.

The term "bioavailability", as used herein means the concentration of an active ingredient (e.g., estradiol) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Pharmacokinetic (PK) indicators that may be used to measure and assess bioavailability are determined by suitable metrics including AUC, Cmax, and, optionally, Tmax.

The term "bioequivalent" means that a test drug product provides similar bioavailability compared to a reference drug product pursuant to the criteria set forth for bioequivalence by the United States Food and Drug Administration, as amended. In general, the bioavailability of an active pharmaceutical ingredient in a bioequivalent drug product is 80 to 125% of the bioavailability of the active pharmaceutical ingredient of the reference drug product concerning AUC and Cmax.

The term "bio-identical hormones", as used herein, means those synthetically-derived compounds which are identical in chemical structure to the hormones naturally produced in vivo. These natural or bio-identical hormones are synthesized from various ingredients to match the chemical structure and effect of estradiol or estrone, or estriol (the 3 primary estrogens).

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 an active pharmaceutical ingredient (e.g., estradiol) over time.

The term "co-administered" as used herein, means that two drug products are administered simultaneously or sequentially on the same or different days.

The term "drug product" as used herein means at least one active pharmaceutical ingredient in combination with at least one excipient and provided in unit dosage form.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients such as carriers, solubilizing agents, 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 "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones synthesized 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 17β-estradiol and E2).

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 triglycerides of such substances. For further illustration, C6-C14, 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 "reference listed drug product" as used herein means Vagifem®.

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 "treatment", as used herein, or a derivative thereof, contemplates partial or complete inhibition of the stated disease state or condition 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, typically a human, to protect the animal from any of the disorders set forth herein, as well as others.

The term, "Tmax" as used herein, refers to the time that it takes for an active pharmaceutical ingredient (e.g., estradiol) and/or estrone blood concentrations to reach the maximum value.

Description

Provided herein are pharmaceutical formulations comprising solubilized estradiol (in various embodiments, at least 90% in solution); providing said formulations do not embrace within the fill one or more of the following components: a hydrophilic gel-forming bioadhesive (e.g., mucoadhesive) agent; a lipophilic agent; a gelling agent for the lipophilic agent, and/or a hydrodispersible agent. The hydrophilic gel-forming bioadhesive agent may provide or exclude one or more of a: carboxyvinylic acid; hydroxypropylcellulose; carboxymethylcellulose; gelatin; xanthane gum; guar gum; aluminum silicate; or mixtures thereof. The lipophilic agent may provide or exclude one or more of a: liquid triglyceride; solid triglyceride (with a melting point of about 35° C.); carnauba wax; cocoa butter; or mixtures thereof. The gelling agent may provide or exclude one or more of a hydrophobic colloidal silica. The hydrodispersible agent may provide or exclude one or more of a: polyoxyethylene glycol; polyoxyethylene glycol 7-glyceryl-cocoate and mixtures thereof.

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. However, in various embodiments, pharmaceutical formulations described herein are prepared as a gel, cream, ointment, transdermal delivery system or like preparation.

Other aspects of the present disclosure include the use of formulations as described herein for the treatment of vulvovaginal atrophy including the treatment of at least one VVA symptom including, for example and without limitation, dryness, itching, soreness, irritation, bleeding and dyspareunia.

Another aspect of the present disclosure provides uses of the formulations described herein for the treatment of estrogen-deficient urinary states.

Another aspect of the present disclosure provides alcohol-free or substantially alcohol-free formulations, and uses thereof. Among others, the formulations offer improved comfort during use, thus tending to enhance patient compliance.

The methods of treatment described herein are generally administered to a human female.

A further aspect of the present invention provides formulations of the present invention wherein circulating blood level concentrations following administration of a formulation of the present invention are bioequivalent to circulating blood level concentrations following administration of the

reference listed drug product, as determined through the completion of a bioequivalence clinical study.

The formulations of the present disclosure may also be vaginally administered with or without the co-administration of an orally administered estrogen-based (or progestin-based or progestin- and estrogen-based) pharmaceutical drug product, or patch, cream, gel, spray, transdermal delivery system or other parenterally-administered estrogen-based pharmaceutical drug product, each of which can include natural, bio-similar, or other synthetic or derived estrogens and/or an administered progestin. As used herein, the term "progestin" means any natural or man-made substance that has pharmacological properties similar to progesterone.

Modulation of circulating estrogen levels provided via the administration of a formulation of the present disclosure, if any, are not intended to be additive to any co-administered estrogen product and its associated circulating blood levels.

The timing of administration of a formulation of the present disclosure may be conducted by any safe means as prescribed by an attending physician. Typically, a patient will insert one capsule intra-vaginally each day for 14 days, then one capsule twice weekly for the remaining time prescribed by such physician. Intra-vaginal insertion may be via the use of an applicator or without an applicator via use of the patient's digits. Use of an applicator or otherwise requires due care as to not puncture or tear surrounding tissue.

Estradiol dosage strengths can vary. For formulations of the present disclosure, estradiol (or estradiol equivalent to the extent such estradiol is in a hydrated or other form requiring compensation therefore) dosage strength of is at least about 1 microgram (mcg), at least about 2.5 mcg; at least about 5 mcg; at least about 10 mcg, from about 1 mcg to about 10 mcg, from about 10 mcg to about 25 mcg, about 1 mcg, about 2.5 mcg, about 5 mcg, about 10 mcg and about 25 mcg. To protect against adverse effects of estradiol, the lowest possible dose should be used for treatment of WA and other states set forth herein. In one embodiment, the dosage is about 10 mcg; in another the dosage is about 25 mcg.

Also provided are soft capsules designed for ease of insertion and to hold the capsule in place until the contents therein are completely released. In various embodiments, softgel capsules in accordance with various embodiments are sized to comfortably fit within a human vagina. Thus, the softgel capsules may comprise any dimension capable of fitting into a human vagina. With reference to FIG. **2**, softgel capsule **200** is illustrated. Softgel capsule **200** comprises fill material **202** and gelatin **204**. Gelatin **204** has a thickness represented by space **208**. Space **208** comprises a distance of 0.108 inches. The distance from one end of softgel capsule **200** to another is represented by space **206**. Space **206** comprises a distance of 0.690 inches. The size of softgel capsule **200** may also be described by the arc swept by a radius of a given length. For example, arc **210**, which is defined by the exterior of gelatin **204**, is an arc swept by a radius of 0.189 inches. Arc **212**, which is defined by the interior of gelatin **204**, is an arc swept by a radius of 0.0938 inches. Arc **214**, which is defined by the exterior of gelatin **204** opposite arc **210**, is an arc swept by a radius of 0.108 inches.

Estradiol can be formulated pursuant to the teachings below. These formulations can be prepared for vaginal insertion in a single unit dosage form or as otherwise specified herein.

In various embodiments, estradiol is solubilized at least once during manufacturing and, in various embodiments, estradiol is solubilized at one point following administration. Solubility may be expressed as a mass fraction (% w/w). As used herein, the term "soluble" or "solubilized" means that the estradiol is: at least about 85% soluble, at least 90% soluble, at least 95% soluble and, frequently, is 100% soluble. % Solubility is expressed herein as a mass fraction (% w/w, also referred to as wt %).

Upon release of the fill into the vaginal canal following insertion of a capsule of the present disclosure, estradiol may be locally absorbed into body tissues.

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.

Solubilized estradiol of the present disclosure is prepared via blending estradiol with a pharmaceutically acceptable solubilizing agent including for example and without limitation, 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 (collectively, "glycerides"). In various embodiments, solubilized estradiol of the present disclosure may also comprise at least one glycol or derivatives thereof or combinations thereof (collectively, "glycols") and/or combinations of such at least one glyceride and glycol. Glycols may be used as solubilizing agents and/or to adjust viscosity and, thus, may be considered thickening agents, as discussed further herein. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient solubilizing agent(s) is/are used to solubilize estradiol.

Pharmaceutically acceptable solubilizing agents include, for example and 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 (polyethylene glycol glyceride) GATTEFOSSE SAS, Saint-Priest, France); which can be used herein as a solubilizing agent or as an anionic surfactant); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride)); SASOL Germany GMBH, Hamburg); MIGLYOL 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 mono- and dicaprylate; a propylene glycol mono- and dicaprate; 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 monoethyl ether)); a diethylene glycol monoethyl ether; glyceryl mono- and di-caprylates; propylene glycol; 1,2,3-propanetriol (glycerol, glycerin, glycerine) esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof. In various embodiments, propylene glycol is used in a cream or ointment.

These solubilizers, as defined herein, and combinations thereof, can be used to form solubilized estradiol formulations of the present disclosure.

At least one anionic and/or non-ionic surfactant can be used in additional embodiments of the presently disclosed formulations containing solubilized estradiol.

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 (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%, 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 39/01 (glycerol esters of saturated C12-C18 fatty acids), GELUCIRE 43/01 (hard fat NF/JPE) and GELUCIRE 50/13 (stearoyl macrogol-32 glycerides EP, stearoyl polyoxyl-32 glycerides NF, stearoyl polyoxylglycerides (USA FDA IIG)). 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%.

Ratios of solubilizing agent(s) to surfactant(s) can vary depending upon the respective solubilizing agent(s) and the respective surfactant(s) and the desired physical characteristics of the resultant formulation of solubilized estradiol. For example and without limitation, CAPMUL MCM and a non-ionic surfactant can be used at ratios including 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Other non-limiting examples include: CAPMUL MCM and GELUCIRE 39/01 can be used in ratios including, for example and without limitation, 6:4, 7:3, and 8:2; CAPMUL MCM and GELUCIRE 43/01 can be used in ratios including, for example and without limitation, 7:3, and 8:2; 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.

Another exemplary non-ionic surfactant includes PEG-6 palmitostearate and ethylene glycol palmitostearate, which is available commercially as TEFOSE 63 ("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 and 9:1. Additional examples of solubilizing agents with non-ionic surfactants include, for example, MIGLYOL 812:GELUCIRE 50/13 and MIGLYOL 812:TEFOSE 63.

Anionic surfactants are well known and can include, for example and without limitation: ammonium lauryl sulfate, dioctyl sodium sulfosuccinate, perfluoro-octane sulfonic acid, potassium lauryl sulfate and sodium stearate.

Non-ionic and/or anionic surfactants can be used alone or 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, should be used to provide solubilized estradiol, upon release from a vaginally-inserted capsule, with consistency of the solubilized estradiol that promotes absorption and minimizes vaginal discharge, particularly when compared to the vaginal discharge frequently occurring following use of a VAGIFEM tablet.

Moreover, the estradiol in the formulations disclosed herein need not be fully solubilized (e.g., at least 98% in solution) at the time of administration/insertion but, rather, needs to be substantially solubilized at the time of release from the vaginally-inserted capsule. As such, the solubilizing agents taught herein, with or without additional excipients other than the solubilizing agents, may be in the liquid or semi-solid form upon administration providing the estradiol containing solubilizing agents and other excipients permit flow to fill capsules. To the extent the estradiol is not fully solubilized at the time of administration/insertion, the estradiol should be substantially solubilized at a temperature of about 37° C. (e.g., body temperature) and, generally, at a pH of about 4.5. In another embodiment, at least one thickening agent may be added to formulations of the present disclosure. The viscosity of the solubilized estradiol may depend upon the solubilizing agent(s) used, the addition of other excipients to the formulation preparation and the desired or required final viscosity required to optimize absorption of the solubilized estradiol. In certain embodiments, the surfactant(s) referenced herein above may provide thickening of the solubilized estradiol such that, upon release, will aid the estradiol in being absorbed by the vaginal mucosa while minimizing vaginal discharge, particularly when compared to the vaginal discharge frequently occurring following use of a Vagifem tablet. Examples of other such thickening agents include, for example and without limitation, hard fats; propylene glycol; a mixture of hard fat EP/NF/JPE, glyceryl ricinoleate, ethoxylated fatty alcohols (ceteth-20, steareth-20) EP/NF (commercially available as OVUCIRE 3460 (mixture of hard fat EP/NF/JPE (and) glyceryl ricinoleate (and) ethoxylated fatty alcohols (ceteth-20, steareth-20) EP/NF) (Gattefosse, Saint-Priest France); a mixture of hard fat EP/NF/JPE, glycerol monooleate (type 40) EP/NF (commercially available as OVUCIRE WL 3264 (mixture of hard fat EP/NF/JPE (and) glycerol monooleate (type 40) EP/NF); a mixture of hard fat EP/NF/JPE, glyceryle monooleate (type 40) EP/NF (commercially available as OVUCIRE WL 2944 (mixture of hard fat EP/NF/JPE (and) glyceryle monooleate (type 40) EP/NF)); and a mixture of various hard fats (commercially available as WITESPOL (hard fats); Sasol Germany GmbH, Hamburg). In various embodiments, the viscosity of formulations in accordance with various embodiments may comprise from about 50 cps to about 1000 cps at 25° C.

In other embodiments, one or more muco-adherent agents may be used to assist with mucosal absorption of the solubilized estradiol. For example, polycarbophil may be used as an acceptable muco-adherent agent. Other agents include, for example and without limitation, poly (ethylene oxide) polymers having a molecular weight of from about 100,000 to about 900,000, chitosans carbopols including polymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol, polymers of acrylic acid and C10-C30 alkyl acrylate crosslinked with allyl pentaerythritol, carbomer homopolymer or copolymer that contains a block copolymer of polyethylene glycol and a long chain alkyl acid ester and the like. Various hydrophilic polymers and hydrogels may be used. In various embodiments, the hydrophilic polymer will swell in response to contact with vaginal or other bodily secretions, enhancing moisturizing and muco-adherent effects. The selection and amount of hydrophilic polymer may be based on the selection and amount of pharmaceutically acceptable solubilizing agent chosen. The

formulation includes 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 formulation may comprise PEG-90M.

In additional embodiments, formulations of the present disclosure may 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 herein incorporated by reference).

In other embodiments, a lubricant may be 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 antioxidant may be used such as, for example and without limitation, butylated hydroxytoluene.

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.

The choice of excipient will, to a large extent, depend on factors such as for example and without limitation, the effect of the excipient on solubility and stability. Additional excipients used in various embodiments may include colorants and preservatives. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may, for example and without limitation, 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 solubilizing agents, excipients and any other additives used in the formulations described herein, each is to be non-toxic, pharmaceutically acceptable and compatible with all other ingredients used.

Further provided herein are methods for the treatment of WA and/or estrogen-deficient urinary states comprising administering to a female, typically a human, in need of treatment a non-toxic and pharmaceutically effective dose of a formulation as further provided herein.

As referenced above, the formulations of the present disclosure are generally vaginally administered via capsules such as soft capsules, including soft gelatin capsules. It is desirable to prepare these soft capsules such that they disintegrate to the extent that substantially all of the solubilized estradiol is released upon disintegration, providing rapid absorption of the solubilized estradiol and minimal to no capsule residue.

Additional objects of the present disclosure include: providing increased patient ease of use while potentially minimizing certain side effects from inappropriate insertion, minimizing incidence of vulvovaginal mycotic infection compared to incidence of vulvovaginal mycotic infection due to usage of Vagifem and other currently available products and; decreased resultant genital pruritus compared to the genital pruritus and/or back pain that may be generated via the use of Vagifem and other currently available products. In illustrative embodiments of the invention, oils are used as solubilizing agents to solubilize estradiol and 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 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/thickening agent 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 (lauroyl macrogol-32 glycerides EP lauroyl polyoxyl-32 glycerides NF lauroyl polyoxylglycerides (USA FDA IIG)) 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. 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 (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/dicaprate).

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.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids (i.e., greater than 50% of the fatty acids are medium chain 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 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	—

So, if an embodiment of this invention is 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. So, if an embodiment of this invention is 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, if an embodiment of this invention is 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 or a similar product.

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.

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 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, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Illustrative Drug Product(s)

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, e.g., lack of or reduction of irritation relative to otherwise similar formulations, lack of or reduction in vaginal discharge of drug product relative to otherwise similar formulations, lack of or reduction of drug product residue inside the vagina, etc. Non-irritating formulations are formulations that in most uses in most patients, when used as prescribed, does not cause pain, soreness, swelling or irritation inside the vagina such that most patients do not go off treatment prior to completion of a prescribed course of therapy. Non-irritating formulations are also formulations that are non-irritating, as described in the preceding sentence, relative to competing products such as tablets, creams, or other intravaginal estrogen delivery forms. Such illustrative drug products are also easily self-administered by a patient in any position by inserting the encapsulated formulation digitally approximately 2 inches into her vagina without a need for an applicator and with minimal to no corresponding discharge.

Formulations that do not create a residue are formulations that are absorbed and/or dispersed without resulting in particulates or other unpleasant remains of non-absorbed or non-dispersed drug product. Again, lack of residue can be relative to competing products.

Formulations that do not discharge from the vagina are formulations that do not flow or drip out of the vagina. Again, lack of discharge can be relative to competing products.

Such embodiments include an encapsulated liquid pharmaceutical formulation for intra-vaginal delivery of estradiol, said formulation comprising estradiol that is at least about 90% solubilized in one or more C6 to C14 fatty acid mono-, di-, or triesters of glycerol and a thickening agent.

A more specific such embodiment is such formulation wherein the estradiol is solubilized (e.g., >90% 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.

In such general and more specific embodiments, the thickening agent can be a non-ionic surfactant, e.g., a polyethylene glycol saturated or unsaturated fatty acid ester or diester. In certain such 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 certain such 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 such embodiments, the non-ionic surfactant employed as the thickening agent is not hydrophilic and has good emulsion properties. An illustrative example of such surfactant is TEFOSE 63, which has a HLB value of about 9-10.

As noted above, such formulations are liquid at room temperature, not gels, hard fats, or any other solid form. The thickening agent serves to increase viscosity, e.g., up to 10,000 cP (10,000 mPa-s), typically to no more than 5000 cP, and more typically to between 50 and 1000 cP. 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., mucoadhesive) 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 thickening agent 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 estradiol, the PK of the encapsulated formulation, the irritancy, vaginal discharge, intravaginal residue, etc., 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 thickening agent, 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 3, below, as "Trial 5".

EXAMPLES

In various embodiments, a vehicle system is created by dissolving an active pharmaceutical ingredient (e.g., estradiol) in one or more pharmaceutically acceptable solubilizing agents. A vehicle system may then be combined with a gel mass to create a final formulation suitable for use in, for example, a vaginal suppository. In that regard, in various embodiments, one or more vehicle systems may be combined with one or more gel masses. Other excipients may also be included in the vehicle system in various embodiments.

Example 1

Formulation: Vehicle System

In various embodiments, estradiol active pharmaceutical ingredient is procured and combined with one or more pharmaceutically acceptable solubilizing agents. Estradiol may be in micronized form or non-micronized form. In various embodiments, the final formulation comprises estradiol in a dosage strength of from about 1 mcg to about 25 mcg.

Estradiol is combined with various pharmaceutically acceptable solubilizing agents in various embodiments. As described above, CAPMUL MCM, MIGLYOL 812, GELUCIRE 39/01, GELUCIRE 43/01, GELUCIRE 50/13, and TEFOSE 63 (\may, alone or in various combinations, be used as a pharmaceutically acceptable solubilizing agent in connection with estradiol.

Solubility of estradiol may affect final formulation stability and uniformity, so care should be taken when selecting an appropriate vehicle system. It is noted that surfactants are typically amphiphilic molecules that contain both hydrophilic and lipophilic groups. A hydrophilic-lipophilic balance ("HLB") number is used as a measure of the ratio of these groups. It is a value between 0 and 20 which defines the affinity of a surfactant for water or oil. HLB numbers are calculated for nonionic surfactants, and these surfactants have numbers ranging from 0-20. HLB numbers >10 have an affinity for water (hydrophilic) and number <10 have an affinity of oil (lipophilic).

In that regard, GELUCIRE 39/01 and GELUCIRE 43/01 each have an HLB value of 1. GELUCIRE 50/13 has an HLB value of 13. TEFOSE 63 has an HLB value of between 9 and 10.

Various combinations of pharmaceutically acceptable solubilizing agents were combined with estradiol and examined. TABLE 1 contains the results. TABLE 1 contains the following abbreviations: CAPMUL MCM ("MCM"), GELUCIRE 39/01 ("39/01"), GELUCIRE 43/01 ("43/01"), GELUCIRE 50/13 ("50/13"), and TEFOSE ("Tefose 63").

TABLE 1

#	Vehicle system	Ratio	Physica state @ Room Temperature	Physical State @ 37° C. after ~30 minutes	Viscosity cps	Melting Time @ 37° C.	Dispersion in water 37° C.
1	MCM:39/01	8:2	Solid	Clear liquid	50@37° C.	Start: 6 min Finish: 12 min	Small oil drops on top
2	MCM:39/01	7:3	Solid	Clear liquid		Start: 9 min Finish: 19 min	
3	MCM:39/01	6:4	Solid	Clear liquid		Start: 20 min Finish: 32 min	
4	MCM:43/01	8:2	Solid	Liquid with solid particles			
5	MCM:43/01	7:3	Solid	Liquid with solid particles			

TABLE 1-continued

#	Vehicle system	Ratio	Physica state @ Room Temperature	Physical State @ 37° C. after ~30 minutes	Viscosity cps	Melting Time @ 37° C.	Dispersion in water 37° C.
6	MCM:50/13	9:1	Liquid/cloudy	Liquid/cloudy	140@25° C.	Clear after 20 min	Uniformly cloudy dispersion
7	MCM:50/13	8:2	Liquid/cloudy	Liquid/cloudy	190@25° C.		Uniformly cloudy dispersion
8	MCM:50/13	7:3	Semisolid	Semisolid			
9	MCM:TEFOSE 63	9:1	Semisolid	Liquid/cloudy	150@25° C.	Start: 1 min Finish: 5 min	Uniformly cloudy dispersion
10	MCM:TEFOSE 63	7:3	Semisolid	Semisolid	240@25° C.		Uniformly cloudy dispersion
11	MCM:TEFOSE 63	8:2	Semisolid	Semisolid	380@25° C.	Semisolid after 30 min at 37° C., doesn't melt at 41° C.	Uniformly cloudy dispersion
12	MIGLYOL 812: 50/13	9:1	Semisolid	Semisolid	140@25° C.		2 phases, oil on top
13	MIGLYOL 812: TEFOSE 63	9:1	Liquid/cloudy	Liquid/cloudy	90@25° C.	Start: 1 min Finish: 5 min	2 phases, oil on top

Vehicle systems in TABLE 1 that were liquid or semisolid at room temperature were tested using a Brookfield viscometer (Brookfield Engineering Laboratories, Middleboro, Mass.) at room temperature. Vehicle systems appearing in TABLE 1 that were solid at ambient temperature were tested using a Brookfield viscometer at 37° C.

Vehicle systems appearing in TABLE 1 that were solid were placed at 37° C. to assess their melting characteristics. The results are in TABLE 1. It is noted that vehicle system 11 in TABLE 1 did not melt at 37° C. or 41° C.

A dispersion assessment of the vehicle systems appearing in TABLE 1 was performed. The dispersion assessment was performed by transferring 300 mg of each vehicle system in 100 ml of 37° C. water, without agitation, and observing for mixing characteristics.

Example 2

Formulation: Gel Mass

In various embodiments, a vehicle system may be combined with a gel mass. A gel mass may comprise, for example, gelatin (e.g., Gelatin, NF (150 Bloom, Type B)), hydrolyzed collagen (e.g., GELITA®, GELITA AG, Eberbach, Germany), glycerin, SORBITOL SPECIAL® (a sorbitan-sorbitol based soft gel plasticizer), and/or other suitable materials in varying proportions. SORBITOL SPECIAL® may be obtained commercially and may tend to act as a plasticizer and humectant.

Gel masses A through F were prepared according to the formulations in TABLE 2. Gel masses A through F differ in the proportion of one or more components, for example.

TABLE 2

Ingredient	Gel A % w/w	Gel B % w/w	Gel C % w/w	Gel D % w/w	Gel E % w/w	Gel F % w/w
Gelatin, NF (150 Bloom, Type B)	41.0	41.0	41.0	41.0	43.0	43.0
Glycerin 99.7%, USP	6.0	6.0	6.0	6.0	18.0	18.0
Sorbitol Special, USP	15.0	15.0	15.0	15.0		
GELITA (hydrolyzed collagen)	3				3.0	
Citric acid		0.1	0.5	1		0.1
Purifed Water	35.0	37.9	37.5	37.0	36.0	38.9
Total	100.0	100.0	100.0	100.0	100.0	100.0
Dissolution gel strips, Avg of 3 (500 ml DH2O, 50 rpm @ 37° C.)	48 min (42, 45, 58)	50 min (50, 51, 50)	75 min (76, 75, 74)	70 min (70, 71, 70)		
Dissolution gel strips, Avg of 3 (500 ml pH 4 buffer, 50 rpm @ 37° C.	70 min				72 min 84 min	82 min

Each gel mass A through F was prepared at a temperature range from about 45° C. to about 85° C. Each molten gelatin mass A through F was cast into a film, dried and cut into strips. The strips were cut into uniform pieces weighing about 0.5 g, with about 0.5 mm thickness. Strips were placed into a USP Type 2 dissolution vessel in either water or pH 4 buffer solution and the time for them to completely dissolve was recorded and listed in TABLE 2. It is noted that gel mass A has the fastest dissolution in both water and pH 4 buffer solution.

Example 3

Formulation: Final Formulation and Encapsulation

Various combinations of vehicle systems from TABLE 1 and gel masses from TABLE 2 were prepared. The combinations are shown in TABLE 3.

TABLE 3

Trial	Vehicle system	Ratio	Batch Size g	Gel
1	MCM:39/01	8:2	750	A
2	MCM:50/13	8:2	750	A
3	MCM:TEFOSE 63	8:2	750	A
4	MCM:TEFOSE 63	8:2	750	B
5	MIGLYOL 812: TEFOSE 63	9:1	750	A

Estradiol was combined with each vehicle system so that about 10 mcg of estradiol was contained within 300 mg of each vehicle system. Batch size was as listed in TABLE 3. To encapsulate the vehicle system, each 300 mg of vehicle system was combined with about 200 mg of the listed gel mass. Thus, for example, in Trial 1, MCM:39/01 in an 8:2 ratio was combined with gel A and 10 mcg of estradiol. In each final dosage, Trial 1 comprised 300 mg of vehicle system, 200 mg of gel mass and 10 mcg of estradiol. It should be noted, however, that in various embodiments the total mass of vehicle system, gel mass, and estradiol may be from about 100 mg to about 1000 mg.

Each combination of vehicle system, estradiol, and gel mass may be suitable for use in, for example, a vaginal suppository.

Example 4

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 4

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Gylcol	75*
Polysorbate 80	36*
TRANSCUTOL HP	141
CAPMUL PG8	31.2

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

In further solubility studies, estradiol was soluble 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 MIGLYOLTRANSCUTOL at 96:4, MIGLYOLLabrasol at 70:30 to 80:20, or MIGLYOLCAPMUL PG8 at 86:14.

Example 5

Process

With reference to FIG. **1**, a method of making a fill material **100** is shown. Step **102** comprises heating a solubilizing agent 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 solubilizing agent may be any such solubilizing agent described herein, for example, CAPMUL MCM.

Step **104** comprises mixing GELUCIRE with the solubilizing agent. As used herein, any form of GELUCIRE may be used in step **104**. For example, one or more of GELUCIRE 39/01, GELUCIRE 43/01, GELUCIRE 50/13. may be used in step **104**. Mixing may be facilitated by an impeller, agitator, or other suitable means. Step **104** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step **106** comprises mixing estradiol into the mixture of the solubilizing agent and GELUCIRE. The estradiol may be mixed in micronized or nonmicronized form. Mixing may occur in a steel tank or other acceptable container. Mixing may be facilitated by an impeller, agitator, or other suitable means. Step **106** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas. In various embodiments, however, the addition of estradiol may be performed prior to step **104**. In that regard, in various embodiments, step **106** is performed prior to step **104**.

Step **110** comprises preparing the gel mass. Any of the gel masses described herein may be used in step **110**. In that regard, gelatin (e.g., Gelatin, NF (150 Bloom, Type B)), hydrolyzed collagen, glycercin, and/or other suitable materials may be combined at a temperature range from about 45° C. to about 85° C. and prepared as a film. Mixing may occur in a steel tank or other acceptable container. 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. Step **112** comprises degasing. The resulting mixture from step **112** may comprise a fill material suitable for production into a softgel capsule.

In step **112**, a soft gel capsule is prepared by combining the material obtained in step **106** with the gel mass of step **110**. The gel film may be wrapped around the material, partially or fully encapsulating it. The gel film may also be injected or otherwise filled with the material obtained in step **106**.

Step **112** may be performed in a suitable die to provide a desired shape. Vaginal soft gel capsules may be prepared in a variety of geometries. For example, vaginal soft gel

capsules may be shaped as a tear drop, a cone with frustoconical end, a cylinder, a cylinder with larger "cap" portion, or other shapes suitable for insertion into the vagina. Vaginal soft gel capsules in accordance with various embodiments may or may not be used in connection with an applicator.

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 a symptom of vulvovaginal atrophy in a female human patient in need thereof, the method comprising administering to the female human an estradiol-containing soft gelatin capsule intravaginally once daily for 14 days and one capsule twice weekly thereafter, the estradiol-containing soft gelatin capsule comprising a gelatin shell surrounding an estradiol-containing liquid fill material, the estradiol-containing liquid fill material comprising one or more C6 to C14 fatty acid mono-, di-, or triesters of glycerol and 1 to 10 mcg of estradiol, wherein the estradiol-containing liquid fill material has a viscosity of between 50 to 1000 cP as measured at 25° C.

wherein:

administering the estradiol-containing soft gelatin capsule intravaginally to the female human in need thereof provides an estradiol AUC and estradiol C_{max} that are each 80% to 125% of the estradiol AUC and estradiol C_{max} obtained upon intravaginal administration of a reference soft gelatin capsule in a reference human female patient, the reference soft gelatin capsule consisting of a soft gelatin shell and a reference liquid fill material within the soft gelatin shell, wherein the reference liquid fill material consists of

approximately 270 mg of a C8 to C10 triglyceride composition containing at least about 80 percent by weight of a mixture of caprylic acid and capric acid;

approximately 30 mg of a surfactant containing a mixture of PEG-6 stearate, PEG-32 stearate, and ethylene glycol palmitostearate; and

1 to 10 mcg of estradiol

further wherein the reference liquid fill material has a viscosity of between 50 to 1000 cP as measured at 25° C.

2. The method of claim **1**, wherein the estradiol-containing fill material further comprises a nonionic surfactant.

3. The method of claim **2**, wherein the nonionic surfactant comprises a mixture of PEG-6 stearate, PEG-32 stearate, and ethylene glycol palmitostearate.

4. The method of claim **1**, wherein the symptom of vulvovaginal atrophy is dyspareunia.

5. The method of claim **1** wherein each capsule disintegrates in the patient's vagina leaving no capsule residue.

6. The method of claim **1**, wherein the estradiol-containing soft gelatin capsule and the reference soft gelatin capsule have substantially similar shapes and sizes.

7. The method of claim **6**, wherein the estradiol-containing soft gelatin capsule and the reference soft gelatin capsule have identical shapes and sizes.

8. The method of claim **7**, wherein the estradiol-containing soft gelatin capsule is shaped with a wider bottom portion and a narrower top portion.

9. The method of claim **7**, wherein the estradiol-containing soft gelatin capsule is in the shape of a tear drop, a cone with a frustoconical end, or a cylinder with a wider cap portion.

10. The method of claim **2**, wherein the nonionic surfactant has an HLB value of or less than about 10.

11. The method of claim **2**, wherein the nonionic surfactant has an HLB value of about 9 to about 10.

12. The method of claim **2**, wherein the nonionic surfactant comprises PEG-6 stearate, PEG-32 stearate, and ethylene glycol palmitostearate.

13. The method of claim **1**, wherein the gelatin shell of the estradiol-containing soft gelatin capsule comprises 150 bloom, Type B gelatin, hydrolyzed collagen, and glycerin.

14. The method of claim **13**, wherein the gelatin shell further comprises a sorbitan-sorbitol based soft gel plasticizer.

15. The method of claim **1**, wherein the estradiol-fill containing material has a mass of about 300 mg.

16. The method of claim **1**, wherein the estradiol-containing soft gelatin capsule has an interior wall surface defining an inner space, wherein a maximal length defined by two points on opposing sides of the interior wall surface is about 0.69 inches.

17. The method of claim **1**, wherein the estradiol-containing soft gelatin capsule has an interior wall surface defining an inner space and an exterior wall surface disposed over the interior wall surface defining a thickness, wherein the thickness measured perpendicular to the interior wall surface and the exterior wall surface is about 0.108 inches.

18. The method of claim **2**, wherein the estradiol-containing fill material comprises a 9:1 ratio of one or more C6 to C14 fatty acid mono-, di-, or triesters of glycerol to nonionic surfactant.

19. The method of claim **1**, wherein administering the reference soft gelatin capsule does not substantially raise circulating estradiol blood levels of the patient following administration.

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