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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

FRESENIUS KABI USA, LLC, Plaintiff, v. ACCORD HEALTHCARE INC., Defendant.	Civil Action No. _____

COMPLAINT

Fresenius Kabi USA, LLC ("Fresenius Kabi" or "Plaintiff"), by its undersigned attorneys, for its complaint against Defendant Accord Healthcare Inc. ("Accord" or "Defendant") alleges as follows:

NATURE OF THE ACTION

1. This is a civil action for patent infringement of U.S. Patent Nos. 10,398,669 ("the '669 patent") and 11,135,190 ("the '190 patent") (collectively, "patents-in-suit"), arising under the United States patent laws, Title 35 United States Code, § 100 *et. seq.*, including 35 U.S.C. §§ 271 and 281.

2. This action relates to Defendant's filing of New Drug Application ("NDA") No. 219224 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C.

§ 355(b)(2), seeking U.S. Food and Drug Administration ("FDA") approval to manufacture, use, import, offer to sell and/or sell levothyroxine sodium injection 100 mcg/mL (1 mL, 2 mL, and 5 mL) ("Accord's NDA Product") before expiration of Fresenius Kabi's patents-in-suit.

THE PARTIES

3. Fresenius Kabi is a corporation organized and existing under the laws of the State of Delaware, having its corporate headquarters at Three Corporate Drive, Lake Zurich, Illinois 60047.

4. On information and belief, Accord is a corporation organized under the laws of the State of North Carolina, having a place of business located at 1009 Slater Road, Suite 210-B, Durham, North Carolina 27703.

JURISDICTION AND VENUE

5. This action for patent infringement arises under 35 U.S.C. § 1 *et. seq.* generally and 35 U.S.C. § 271 specifically.

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

7. Accord previously consented to personal jurisdiction in a prior lawsuit filed in this District involving the same parties and a generic levothyroxine sodium product, *Fresenius Kabi USA, LLC v. Accord Healthcare Inc.*, 22-cv-6341-MAS-RLS. In addition, Accord, through its counsel, consented to jurisdiction and venue in New Jersey for purposes of this action, prior to the filing of this Complaint.

8. Moreover, Accord has litigated previous Hatch-Waxman patent litigation disputes in the District of New Jersey. *See, e.g.*, *Fresenius Kabi USA, LLC v. Accord Healthcare Inc.*, C.A. No. 22-06341, Dkt. 1 (D.N.J. Oct. 28, 2022); *Janssen Pharmaceuticals, Inc. et al. v. Accord*

Healthcare Inc. et al., C.A. No. 22-00856, Dkt. 5 (D.N.J. Feb. 18, 2022); *Eagle Pharmaceuticals, Inc. et al. v. Accord Healthcare Inc.*, C.A. No. 19-09031, Dkt. 11 (D.N.J. Apr. 15, 2019).

9. This Court also has personal jurisdiction over Accord because Accord's contacts within this Judicial District are continuous and systematic. On information and belief, Accord develops, manufactures, seeks approval for, and sells FDA-approved generic pharmaceutical drugs that are regularly marketed, distributed, and sold in New Jersey and throughout the United States. Thus, on information and belief, Accord does substantial business in New Jersey, derives substantial revenue from New Jersey, and engages in other persistent courses of conduct in New Jersey. These continuous and systematic contacts, including but not limited to those described above and below, are more than sufficient for this Court to exercise personal jurisdiction over Accord.

10. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b) at least because, upon information and belief, Accord is registered to do business in New Jersey with an entity ID of No. 5003815. Upon information and belief, based upon Accord's registration to do business in New Jersey and its intended sales and distribution of products in New Jersey, Accord also has a regular and established place of business in this Judicial District. On information and belief, Accord representatives make contacts to this Judicial District for the purpose of marketing and selling Accord's pharmaceutical products.

11. Venue is proper in this Court because, among other things, Accord, through its counsel, consented to jurisdiction and venue in New Jersey for purposes of this action, prior to the filing of this Complaint.

THE PATENTS-IN-SUIT

12. The FDA issues a publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book").

13. Fresenius Kabi is the holder of NDA No. 210632 for Levothyroxine Sodium injection, which the FDA approved on April 11, 2019. Fresenius Kabi currently sells Levothyroxine Sodium injection in the United States.

14. The '669 patent, entitled "Levothyroxine Liquid Formulations," was duly and legally issued on September 3, 2019, naming Arunya Usayapant and Basma M. Ibrahim as the inventors. A true and correct copy of the '669 patent is attached hereto as Exhibit A.

15. Fresenius Kabi is the assignee and lawfully owns all right, title, and interest in the '669 patent, including the right to sue and to recover for infringement thereof.

16. In accordance with 21 U.S.C. § 355(b)(1), the '669 patent is listed in the Orange Book in connection with approved NDA No. 210632 as a patent claiming Fresenius Kabi's NDA drug product or a method of using that drug and "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."

17. According to the Orange Book, the '669 patent is currently not due to expire until December 1, 2036.

18. The '190 patent, entitled "Levothyroxine Liquid Formulations," was duly and legally issued on October 5, 2021, naming Arunya Usayapant and Basma M. Ibrahim as the inventors. A true and correct copy of the '190 patent is attached hereto as Exhibit B.

19. Fresenius Kabi is the assignee and lawfully owns all right, title, and interest in the '190 patent, including the right to sue and to recover for infringement thereof.

20. In accordance with 21 U.S.C. § 355(b)(1), the '190 patent is listed in the Orange Book in connection with approved NDA No. 210632 as a patent claiming Fresenius Kabi's NDA drug product or a method of using that drug and "with respect to which a claim of patent

infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."

21. According to the Orange Book, the '190 patent is currently not due to expire until December 1, 2036.

ACCORD'S NDA NO. 219224

22. On information and belief, Accord submitted NDA No. 219224 to the FDA under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, seeking FDA approval to engage in the commercial manufacture, use, importation, offer for sale, or sale of Accord's NDA Product.

23. On information and belief, Accord is the owner of NDA No. 219224.

24. In submitting its NDA No. 219224, Accord was required to identify any drug upon which the NDA relied for approval of Accord's NDA Product and to submit a certification regarding the patents that are listed in the Orange Book for this drug. 21 U.S.C. § 355(b)(2).

25. On information and belief, Accord identified NDA No. 210632 as the reference listed drug upon which Accord's NDA No. 219224 relied in seeking approval. The Orange Book identifies Fresenius Kabi as the holder of NDA No. 210632.

26. On information and belief, Accord submitted a certification pursuant to Section 505(b)(2)(A)(iv) ("Paragraph IV Certification") that the patents listed for NDA No. 210632 are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Accord's NDA Product.

27. Accord sent a letter dated March 14, 2024 ("the Notice Letter"), purporting to be a Notice of Certification for NDA No. 219224.

28. In the Notice Letter, Accord indicated that the active ingredient of Accord's NDA Product is levothyroxine sodium. Accord further indicated that the proposed strength is 100

mcg/mL (1 mL, 2 mL and 5 mL). Accord also stated that the proposed dosage form of Accord's NDA Product is a solution for parenteral injection.

29. On information and belief, NDA No. 219224 seeks approval of a generic levothyroxine sodium injection product that is the same, or substantially the same, as commercially marketed and approved product that is the subject of Fresenius Kabi's NDA.

30. On information and belief, if NDA No. 219224 is approved by the FDA before the expiration of the patents-in-suit, Accord will begin manufacturing, using, importing, offering for sale, and/or selling Accord's NDA Product in the United States despite the patents-in-suit.

31. On information and belief, Accord was aware of the patents-in-suit when it submitted NDA No. 219224 to the FDA, which NDA contained the above-described paragraph IV certification(s) concerning the patents-in-suit.

COUNT I
INFRINGEMENT OF U.S. PATENT NO. 10,398,669

32. Fresenius Kabi incorporates and realleges all the above paragraphs.

33. The submission of NDA No. 219224 was an act of infringement by Accord of one or more claims of the '669 patent under 35 U.S.C. § 271(e)(2). In the event that Accord commercially manufactures, imports, uses, offers for sale, or sells Accord's NDA Product, said actions would constitute infringement of the '669 patent under 35 U.S.C. § 271(a).

34. On information and belief, Accord's NDA Product is covered by each claim of the '669 patent.

35. On information and belief, Accord's commercial manufacture, importation, use, sale, and/or offer for sale of Accord's NDA Product before the expiration of the '669 patent would directly infringe the claims of the '669 patent.

36. The ’669 patent has seventeen (17) claims directed to a liquid formulation containing levothyroxine. Independent claim 1 of the ’669 patent is directed to:

> A liquid formulation comprising
>
> levothyroxine or a pharmaceutically acceptable salt thereof;
> a stabilizing agent comprising tromethamine;
> not more than 2% liothyronine (T3); and
> water;
> wherein the formulation retains at least about 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for 12 months at 25±2 °C., and retains at least about 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for 2 months at 40±2 °C.

37. Before this lawsuit was filed, and pursuant to an Offer of Confidential Access, Accord produced its NDA, along with a confidentiality designation. Information contained therein confirms that Accord meets each and every limitation of at least claim 1 of the ’669 patent, either literally or under the doctrine of equivalents.

38. On information and belief, unless enjoined by this Court, Accord plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Accord’s NDA Product with its proposed labeling immediately following approval of NDA No. 219224 and before the expiration of the ’669 patent.

39. On information and belief, unless enjoined by this Court, upon FDA approval of Accord’s NDA No. 219224, Accord will infringe, either literally or under the doctrine of equivalents, one or more claims of the ’669 patent by engaging in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Accord’s NDA Product.

40. On information and belief, Accord has been aware of the existence of the ’669 patent since before the submission of NDA No. 219224.

41. On information and belief, Accord has no reasonable basis for believing that Accord's NDA Product will not infringe one or more valid claims of the '669 patent and no reasonable basis for believing that the infringed claims are invalid.

42. This case is "exceptional," as that term is used in 35 U.S.C. § 285.

43. The acts of infringement by Accord set forth above will cause Fresenius Kabi irreparable harm for which it has no adequate remedy at law, and those acts will continue unless enjoined by this Court.

44. Fresenius Kabi is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the FDA set the effective date of approval for Accord's NDA No. 219224 to be a date that is not any earlier than the expiration date of the '669 patent, including any extensions of that date.

COUNT II
INFRINGEMENT OF U.S. PATENT NO. 11,135,190

45. Fresenius Kabi incorporates and realleges all the above paragraphs.

46. The submission of NDA No. 219224 was an act of infringement by Accord of one or more claims of the '190 patent under 35 U.S.C. § 271(e)(2). In the event that Accord commercially manufactures, imports, uses, offers for sale, or sells Accord's NDA Product, said actions would constitute infringement of the '190 patent under 35 U.S.C. § 271(a).

47. On information and belief, Accord's NDA Product is covered by each claim of the '190 patent.

48. On information and belief, the commercial importation, manufacture, use, sale, and/or offer for sale of Accord's NDA Product by Accord before the expiration of the '190 patent would directly infringe the claims of the '190 patent.

49. The ’190 patent has 16 claims directed to levothyroxine compositions. Independent claim 1 of the ’190 patent is directed to:

> A pharmaceutical product comprising a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, a stabilizing agent comprising an amine selected from one or more of tromethamine, bis(2-hydroxyethyl)-imino-tri(hydroxymethyl)methane, monoethanolamine, triethanolamine, 2-amino-2-methyl-1,3-propanediol, 2-dimethylamino-2-methyl-1-propanediol, 2-amino-2-ethylpropanol, 2-amino-1-butanol, and 2-amino-2-mythyl-1-propanol, and water, wherein the formulation retains at least 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for two months at 40℃. and retains at least 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for at least 12 months at room temperature.

50. Before this lawsuit was filed, and pursuant to an Offer of Confidential Access, Accord produced its NDA, along with a confidentiality designation. Information contained therein confirms that Accord meets each and every limitation of at least claim 1 of the ’669 patent, either literally or under the doctrine of equivalents.

51. On information and belief, unless enjoined by this Court, Accord plans and intends to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Accord’s NDA Product with its proposed labeling immediately following approval of NDA No. 219224 and before the expiration of the ’190 patent.

52. On information and belief, unless enjoined by this Court, upon FDA approval of Accord’s NDA No. 219224, Accord will infringe, either literally or under the doctrine of equivalents, one or more of the claims of the ’190 patent by engaging in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Accord’s NDA Product.

53. On information and belief, Accord has been aware of the existence of the ’190 patent since before the submission of NDA No. 219224.

54. On information and belief, Accord has no reasonable basis for believing that Accord's NDA Product will not infringe one or more valid claims of the '190 patent and no reasonable basis for believing that the infringed claims are invalid.

55. This case is "exceptional," as that term is used in 35 U.S.C. § 285.

56. The acts of infringement by Accord set forth above will cause Fresenius Kabi irreparable harm for which it has no adequate remedy at law, and those acts will continue unless enjoined by this Court.

57. Fresenius Kabi is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the FDA set the effective date of approval for Accord's NDA No. 219224 to be a date that is not any earlier than the expiration date of the '190 patent, including any extensions of that date.

PRAYER FOR RELIEF

WHEREFORE, Fresenius Kabi respectfully requests the following relief:

A. Judgment in favor of Fresenius Kabi against Accord;

B. Judgment, pursuant to 35 U.S.C. § 271(e)(2) and 35 U.S.C. § 271(a), that Accord has infringed the '669 patent and the '190 patent by the submission of NDA No. 219224, and that the importation, sale, offer for sale, use, and/or manufacture of Accord's NDA Product, in the United States, would infringe the '669 patent and the '190 patent;

C. Judgment, pursuant to 35 U.S.C. § 271(e)(4)(A) and other provisions of 35 U.S.C. § 271, that the effective date of approval of NDA No. 219224 shall be a date not earlier than the date of expiration of the '669 patent and the '190 patent plus any additional periods of exclusivity;

D. A preliminary and permanent injunction, pursuant to 35 U.S.C. §§ 271 and 283 and Federal Rule of Civil Procedure 65, enjoining Accord, and its officers, partners, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities

and all other persons acting in concert, participation, or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Accord's NDA Product, before the expiration of the '669 patent and the '190 patent and any additional periods of exclusivity;

E. A declaration that this is an exceptional case and an award to Fresenius Kabi of its reasonable attorneys' fees and expenses, as provided by 35 U.S.C. §§ 271(e)(4) and 285;

F. Damages or other monetary relief, including prejudgment interest, if Accord engages in the commercial manufacture, use, offering to sell, sale, marketing, distribution, or importation of Accord's NDA Product, or any other products that would infringe the '669 patent and the '190 patent prior to the expiration of the '669 patent and the '190 patent, respectively;

G. An award of pre-judgment and post-judgment interest on each and every award;

H. An award of Fresenius Kabi's taxable costs in bringing and prosecuting this action; and

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

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Dated: April 26, 2024

EXHIBIT A

US010398669B2

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

(10) **Patent No.: US 10,398,669 B2**
(45) **Date of Patent: *Sep. 3, 2019**

(54) **LEVOTHYROXINE LIQUID FORMULATIONS**

(71) Applicant: **Fresenius Kabi USA, LLC**, Lake Zurich, IL (US)

(72) Inventors: **Arunya Usayapant**, Mundelein, IL (US); **Basma M. Ibrahim**, Lincolnshire, IL (US)

(73) Assignee: **Fresenius Kabi USA, LLC**, Lake Zurich, IL (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.: **15/700,258**

(22) Filed: **Sep. 11, 2017**

(65) **Prior Publication Data**

US 2018/0153838 A1 Jun. 7, 2018

Related U.S. Application Data

(63) Continuation of application No. 15/366,864, filed on Dec. 1, 2016, now Pat. No. 9,782,376.

(51) **Int. Cl.**

A61K 31/198	(2006.01)
A61K 9/08	(2006.01)
A61K 47/18	(2017.01)
A61K 47/02	(2006.01)
A61K 9/00	(2006.01)
A61K 33/18	(2006.01)

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

CPC ***A61K 31/198*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 33/18*** (2013.01); ***A61K 47/02*** (2013.01); ***A61K 47/18*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/33

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,035,974	A	5/1962	Israel
5,951,989	A	9/1999	Heymann
6,383,471	B1	5/2002	Chen et al.
6,458,842	B1	10/2002	Dickinson et al.
6,645,526	B2	11/2003	Hanshew, Jr. et al.
6,706,255	B2	3/2004	Dickinson et al.
6,936,274	B2	8/2005	Hanshew, Jr. et al.
7,052,717	B2	5/2006	Hanshew, Jr. et al.
7,195,779	B2	3/2007	Hanshew, Jr. et al.
7,723,390	B2	5/2010	Garavani et al.
7,858,663	B1	12/2010	Bristol et al.
8,318,712	B2	11/2012	Pierres et al.
8,759,572	B2	6/2014	Viscardi et al.
8,779,000	B1	7/2014	Parikh et al.
9,006,289	B2	4/2015	Jiang et al.
9,050,307	B2	6/2015	Psarrakis et al.
9,168,238	B2	10/2015	Jiang et al.
9,168,239	B2	10/2015	Jiang et al.
9,345,772	B1	5/2016	Parikh et al.
9,428,444	B2	8/2016	Rao et al.
2005/0059574	A1	3/2005	Klein et al.
2009/0270507	A1	10/2009	Pierres et al.
2016/0331711	A1	11/2016	Parikh et al.
2018/0214374	A1	8/2018	Chandrashekhar et al.

FOREIGN PATENT DOCUMENTS

WO	WO 2015/151013 A1	10/2015
WO	WO 2017/013591 A1	1/2017
WO	WO 2017/077476 A1	5/2017

OTHER PUBLICATIONS

Pramanick et al., "Excipient Selection in Parenteral Formulation Development," *Pharma Times* 45(3): 65-77 (2013).

European Patent Office, International Search Report in International Application No. PCT/US2017/062019 (dated Feb. 21, 2018).

European Patent Office, Written Opinion in International Application No. PCT/US2017/062019 (dated Feb. 21, 2018).

Bernareggi et al., "Oral Liquid Formulation of Levothyroxine is Stable in Breakfast Beverages and May Improve Thyroid Patient Compliance," *Pharmaceutics*, 5: 621-633 (2013).

Collier et al., "Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate," *AAPS PharmSciTech*, 11(2): 818-825 (2010).

Kannamkumarath et al., "Determination of Levothyroxine and its Degradation Products in Pharmaceutical Tablets by HPLC-UV-ICP-MS," *J. Anal. At. Spectrom.*, 19: 107-113 (2004).

Kazemifard et al., "Identification and Quantitation of Sodium-Thyroxine and its Degradation Products by LC Using Electrochemical and MS Detection," *J. Pharm. Biomed. Anal.*, 25: 697-711 (2001).

Patel, "The Effect of Formulation and Processing Variables on the Stability of Levothyroxine Sodium Tablets," Dissertation submitted to Univ. Cincinnati Coll. of Pharmacy: pp. 1-151 (May 2003).

Patel et al., "The Effect of Excipients on the Stability of Levothyroxine Sodium Pentahydrate Tablets," *Int. J. Pharm.*, 264: 35-43 (2003).

Remington Pharmaceutical Science, 17th Edition, Alfonso R. Gennaro, Editor, Mack Publishing Company, Easton, PA, USA, pp. 836-837, 1455-1472 (1985).

Schering Corp., Prescribing Information for LEVENTA Levothyroxine Sodium Solution: pp. 1-5 (Oct. 2010).

Shah et al., "Stability Indication Validated HPLC Method for Quantification of Levothyroxine with Eight Degradation Peaks in the Presence of Excipients," *Int. J. Pharm.*, 360: 77-82 (2008).

(Continued)

Primary Examiner — San Ming R Hui

(74) *Attorney, Agent, or Firm* — Leydig, Voit & Mayer, Ltd.

(57) **ABSTRACT**

The present invention is directed to a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof. The formulation of the present invention includes tromethamine, sodium iodide, and water and has a pH of about 9.0 to about 11.5. The liquid formulation according to the invention is stable and ready-to-use.

17 Claims, No Drawings

(56) **References Cited**

OTHER PUBLICATIONS

Stadalman et al., "Stability of Levothyroxine Sodium 0.4 µg/mL in 0.9% Sodium Chloride Injection," *Prog. Transplant.*, 19(4): 354-356 (2009).
Strong et al., "Stability of Levothyroxine in Sodium Chloride for IV Administration," *Can. J. Hosp. Pharm.*, 63(6): 437-443 (2010).
United States Pharmacopeial Convention, "Levothyroxine Sodium," United States Pharmacopeia and National Formulary (Revision Bulletin): pp. 1-3 (Oct. 2010).
Won, "Kinetics and Degradation of Levothyroxine in Aqueous Solution and in Solid State," *Pharm. Res.*, 9(1): 131-137 (1992).

LEVOTHYROXINE LIQUID FORMULATIONS

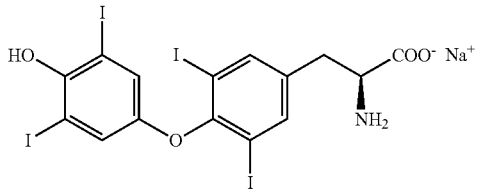
CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a continuation of co-pending U.S. patent application Ser. No. 15/366,864, filed Dec. 1, 2016, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

Levothyroxine sodium for injection is a sterile lyophilized product for parenteral administration of levothyroxine sodium for thyroid replacement therapy. Levothyroxine sodium for injection is particularly useful when thyroid replacement is needed on an urgent basis, for short term thyroid replacement, and/or when oral administration is not possible, such as for a patient in a state of myxedema coma.

Full chemical names for levothyroxine sodium include 4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodo-L-phenylalanine sodium, and L-tyrosine-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-monosodium salt. Levothyroxine sodium has a molecular weight of approximately 798.85 and the following chemical structure:



Conventional formulations of levothyroxine sodium for injection are preservative-free lyophilized powders containing levothyroxine sodium and the excipients mannitol, sodium phosphate buffer, and sodium hydroxide. Administration of the conventional formulations involve reconstitution of the lyophilized powder in 0.9% sodium chloride injection (USP) to provide an injectable solution.

However, use of the conventional lyophilized formulations requires reconstitution or dilution by healthcare practitioners prior to use. Once reconstituted, the levothyroxine sodium solutions have a limited stability, and must be used within a few hours of reconstitution. In addition, contaminants may be introduced into the solutions during the reconstitution process, thereby compromising patient safety.

It has been shown that levothyroxine in oral tablets and in aqueous solutions undergoes degradation. Major degradation products of levothyroxine are known to include 3,3',5-triiodothyronine (T3) 3,5-diiodothyronine (T2) 3,3',5,5'-tetraiodothyroacetic acid (TTAA4) 3,3',5-triiodothyroacetic acid (TTAA3) and 3,5-diiodothyroacetic acid (TTAA2) (Kannamkumarath et al., *J. Anal. At. Spectrom.,* 2004, 19: 107-113 and Patel et al., *Int. J. Pharm.,* 2003, 264: 35-43)). 3,3',5-triiodothyronine, known as liothyronine or T3, is a major degradant. Aqueous solutions of levothyroxine sodium have been shown to be more stable at basic pH than at acidic pH, but significant degradation of levothyroxine sodium also has been shown to occur at basic pH (Patel et al., *Int. J. Pharm.,* 2003, 264: 35-43).

Thus, there remains a need in the art for a ready-to-use injectable formulation of levothyroxine sodium that exhibits storage stability.

BRIEF SUMMARY OF THE INVENTION

The invention provides a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, and water, wherein the formulation has a pH of about 9.0 to about 11.5.

The invention also provides a liquid formulation comprising (a) levothyroxine or a pharmaceutically acceptable salt thereof in a concentration of about 20 mcg/mL to about 100 mcg/mL, (b) tromethamine in a concentration of about 5 mg/mL to about 20 mg/mL, (c) sodium iodide in a concentration of about 100 mcg/mL to about 300 mcg/mL, (d) sodium chloride, and (e) water, wherein the formulation has a pH of about 9.8 to about 10.8.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, and water, wherein the formulation has a pH of about 9.0 to about 11.5. The liquid formulation according to the invention is stable and ready-to-use.

As used herein, a "ready-to-use" formulation is a sterile, injectable formulation that is not reconstituted from a solid by a healthcare provider prior to use. Rather, a ready-to-use formulation is supplied by a pharmaceutical manufacturer in a suitable container (e.g., vial, syringe, bag, container) in liquid form. In some embodiments, a ready-to-use formulation is an injectable formulation that is administered to a subject without dilution. In other embodiments, a ready-to-use formulation is a concentrated, liquid solution that must be diluted prior to administration to a subject. Thus, in some embodiments, the formulation of the present invention can be further diluted in an appropriate diluent such as, for example, WFI (water for injection), 0.9% sodium chloride, or 5% dextrose to a lower levothyroxine concentration.

The formulation according to the present invention is stable. As used herein, the terms "stable" and "stability" encompass any characteristic of the formulation which may be affected by storage conditions including, without limitation, potency, total impurities, levothyroxine degradation products, specific optical rotation, optical purity, water content, appearance, viscosity, sterility, and color and clarity. The storage conditions which may affect stability include, for example, duration of storage, temperature, humidity, and/or light exposure.

In certain embodiments, a stable levothyroxine formulation refers to a formulation that retains at least about 90%, or about least about 95%, or at least about 96%, or at least about 98%, of the labeled concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage under typical and/or accelerated conditions. In further embodiments, a stable levothyroxine formulation refers to less than about 15% (area percent), or less than about 10% (area percent), or less than about 7% (area percent), or less than about 5% (area percent), or less than about 2% (area percent) of levothyroxine-related impurities are present after storage under typical and/or accelerated conditions.

In some embodiments, the liquid formulation of the invention is stable for at least 12 months, at least 18 months, at least 24 months, or at least 36 months at refrigerated temperature (e.g., at 5±2° C.). In other embodiments, the liquid formulation of the invention is stable for at least 12

months, at least 18 months, at least 24 months, or at least 36 months at room temperature (e.g., at 25±2° C.).

Methods for determining the stability of a formulation of the invention with respect to a given parameter are well-known to those of skill in the art. For example, individual impurities and total impurities can be assessed by high-performance liquid chromatography (HPLC) or thin layer chromatography (TLC). Unless otherwise indicated to the contrary, a percentage amount of liothyronine, other individual impurities, or total impurities reported herein in the formulation is determined by a peak area percent method using HPLC.

The formulation comprises levothyroxine or any pharmaceutically acceptable salt thereof. Preferably, the formulation comprises levothyroxine sodium. In an embodiment, the levothyroxine sodium is levothyroxine sodium pentahydrate, which is the sodium salt of the levo-isomer of thyroxine, an active physiological substance found in the thyroid gland.

When the formulation comprises levothyroxine sodium, the levothyroxine sodium can be present in the formulation in any suitable concentration. Typically, levothyroxine sodium can be present in the formulation at a concentration of about 5 mcg/mL (micrograms/milliliter) or more, for example, about 10 mcg/mL or more, about 15 mcg/mL or more, about 20 mcg/mL or more, about 25 mcg/mL or more, about 30 mcg/mL or more, about 35 mcg/mL or more, about 40 mcg/mL or more, or about 45 mcg/mL or more.

Alternatively, levothyroxine sodium can be present in the formulation at a concentration of about 500 mcg/mL or less, for example, about 450 mcg/mL or less, about 400 mcg/mL or less, about 350 mcg/mL or less, about 300 mcg/mL or less, about 250 mcg/mL or less, about 200 mcg/mL or less, or about 150 mcg/mL or less.

Levothyroxine sodium can be present in the formulation in a concentration bounded by any two of the aforementioned endpoints. For example, levothyroxine sodium can be present in the formulation in a concentration of about 5 mcg/mL to about 500 mcg/mL, for example, about 10 mcg/mL to about 450 mcg/mL, about 15 mcg/mL to about 400 mcg/mL, about 20 mcg/mL to about 350 mcg/mL, about 25 mcg/mL to about 300 mcg/mL, about 30 mcg/mL to about 300 mcg/mL, about 35 mcg/mL to about 300 mcg/mL, about 40 mcg/mL to about 300 mcg/mL, about 45 mcg/mL to about 300 mcg/mL, or about 50 mcg/mL to about 250 mcg/mL, or about 20 mcg/mL to about 100 mcg/mL.

In a preferred embodiment, levothyroxine sodium is present at a concentration of about 20 mcg/mL. In another preferred embodiment, levothyroxine sodium is present at a concentration of about 40 mcg/mL. In yet another preferred embodiment, levothyroxine sodium is present at a concentration of about 100 mcg/mL.

The formulation can be provided in any suitable volume. In some embodiments, the volume of the formulation is about 0.5 mL or more, e.g., about 1 mL or more, about 3 mL or more, about 5 mL or more, about 8 mL or more, about 10 mL or more, about 20 mL or more, or about 50 mL or more. In other embodiments, the volume of the formulation is about 200 mL or less, e.g., about 150 mL or less, about 100 mL or less, about 50 mL or less, about 30 mL or less, about 15 mL or less, about 10 mL or less, or about 5 mL or less. The formulation can be provided in a volume bounded by any two of the aforementioned endpoints. For example, the formulation can be provided in a volume of about 1 mL to about 200 mL, about 1 mL to about 50 mL, about 3 mL to about 30 mL, about 5 mL to about 100 mL, or about 3 mL to about 10 mL. In certain preferred embodiments, the volume of the formulation is about 5 mL. One of ordinary skill in the art can readily select an appropriate container based upon the volume of the formulation.

The formulation comprises at least one stabilizing agent. The stabilizing agent serves to stabilize levothyroxine or a pharmaceutically acceptable salt thereof in the liquid formulation.

In some embodiments, the stabilizing agent is an amine. Non-limiting examples of suitable amines include tromethamine (i.e., 2-amino-2-hydroxymethyl-propane-1,3-diol or Tris), bis(2-hydroxyethyl)-imino-tris(hydroxymethyl)methane (Bis-tris or Bis-tris methane), monoethanolamine, diethanolamine, triethanolamine, 2-amino-2-methyl-1,3-propanediol, 2-dimethylamino-2-methyl-1-propanediol, 2-amino-2-ethylpropanol, 2-amino-1-butanol, and 2-amino-2-methyl-1-propanol. Preferably, the amine is tromethamine.

The amine can be present in the formulation in any suitable concentration. Typically, the amine can be present in the formulation at a concentration of about 1 mg/mL (milligram/milliliter) or more, for example, about 5 mg/mL or more, about 10 mg/mL or more, about 15 mg/mL or more, or about 20 mg/mL or more. Alternatively, the amine can be present in the formulation at a concentration of about 50 mg/mL or less, for example, about 45 mg/mL or less, about 40 mg/mL or less, about 35 mg/mL or less, about 30 mg/mL or less, about 25 mg/mL or less, or about 20 mg/mL or less.

Thus, the amine can be present in the formulation in a concentration bounded by any two of the aforementioned endpoints. For example, the amine can be present in the formulation in a concentration of about 1 mg/mL to about 50 mg/mL, for example, about 1 mg/mL to about 50 mg/mL, about 5 mg/mL to about 45 mg/mL, about 5 mg/mL to about 40 mg/mL, about 5 mg/mL to about 35 mg/mL, about 5 mg/mL to about 30 mg/mL, about 5 mg/mL to about 25 mg/mL, or about 5 mg/mL to about 20 mg/mL. In a preferred embodiment, the amine is tromethamine present at a concentration of about 20 mg/mL. In another preferred embodiment, the amine is tromethamine present at a concentration of about 10 mg/mL.

In some embodiments, the stabilizing agent is a salt of iodine, such as sodium iodide or potassium iodide. In some embodiments, the formulation comprises sodium iodide at a concentration of about 10 mcg/mL or more, e.g., 25 mcg/mL or more, 50 mcg/mL or more, 75 mcg/mL or more, 100 mcg/mL or more, 125 mcg/mL or more, 150 mcg/mL or more, 175 mcg/mL or more, or 200 mcg/mL or more. In other embodiments, the formulation comprises sodium iodide at a concentration of about 500 mcg/mL or less, e.g., 450 mcg/mL or less, 400 mcg/mL or less, 350 mcg/mL or less, 300 mcg/mL or less, 250 mcg/mL or less, 200 mcg/mL or less, 175 mcg/mL or less, or 150 mcg/mL or less.

Thus, the sodium iodide can be present in the formulation in a concentration bounded by any two of the aforementioned endpoints. For example, the sodium iodide can be present in the formulation in a concentration of about 10 mcg/mL to about 500 mcg/mL, for example, about 50 mcg/mL to about 400 mcg/mL, about 100 mcg/mL to about 300 mcg/mL, about 125 mcg/mL to about 300 mcg/mL, about 125 mcg/mL to about 250 mcg/mL, about 125 mcg/mL to about 200 mcg/mL, about 125 mcg/mL to about 175 mcg/mL, or about 125 mcg/mL to about 150 mcg/mL. In a preferred embodiment, the sodium iodide is present at a concentration of about 140 mcg/mL.

The formulation can comprise one, two, or three or more stabilizing agents. In certain embodiments, the formulation comprises an amine and a salt of iodine, preferably tromethamine and sodium iodide. In some embodiments, the formulation comprises about 10 mg/mL tromethamine and about 140 mcg/mL sodium iodide.

The formulation comprises an isotonicity adjuster. Non-limiting examples of suitable isotonicity adjusters include sodium chloride, potassium chloride, dextrose, glycerin, and mannitol. In a preferred embodiment, the isotonicity adjuster is sodium chloride.

The isotonicity adjuster can be present at any suitable concentration. In some embodiments, the isotonicity adjuster is present at a concentration that renders the formulation isotonic or approximately isotonic with cells (e.g., red blood cells) and/or isotonic or approximately isotonic to blood plasma.

The formulation optionally comprises a pH adjuster. The pH adjuster can be any suitable pH adjuster, for example, the pH adjuster can be sodium hydroxide, potassium hydroxide, hydrochloric acid, or combinations thereof. In a preferred embodiment, the pH adjuster is sodium hydroxide, hydrochloric acid, or a combination thereof.

The formulation can have any suitable pH. Typically, the formulation can have a pH of about 9.0 or more including, for example, about 9.0 or more, about 9.2 or more, about 9.4 or more, about 9.6 or more, about 9.8 or more, about 10.0 or more, or about 10.2 or more. Alternatively, the formulation can have a pH of about 11.5 or less including, for example, about 11.3 or less, about 11.1 or less, about 11.0 or less, about 10.9 or less, about 10.8 or less, about 10.7 or less, about 10.6 or less, or about 10.5 or less.

The formulation can have a pH bounded by any two of the above endpoints recited for the formulation. For example the formulation can have a pH of about 9.0 to about 11.5 including, for example, about 9.0 to about 11.0, about 9.2 to about 10.8, about 9.2 to about 10.8, about 9.4 to about 10.8, about 9.6 to about 10.8, about 9.8 to about 10.8, about 10.0 to about 10.8, about 10.0 to about 10.7, about 10.0 to about 10.5, or about 10.2 to about 10.6.

Tromethamine has a buffering range of about 7 to about 9. In a preferred embodiment, the pH of the formulation is about 9.8 to about 10.8, which is above the buffering range of tromethamine. While not wishing to be bound by any particular theory, it is believed that tromethamine exerts a stabilizing effect on levothyroxine by a mechanism unrelated to buffering of the formulation.

In a preferred embodiment, the formulation comprises (a) levothyroxine or a pharmaceutically acceptable salt thereof in a concentration of about 20 mcg/mL to about 100 mcg/mL, (b) tromethamine in a concentration of about 5 mg/mL to about 20 mg/mL, (c) sodium iodide in a concentration of about 100 mcg/mL to about 300 mcg/mL, (d) sodium chloride, and (e) water, wherein the formulation has a pH of about 9.8 to about 10.8.

The formulation that comprises levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, sodium chloride, and water may further include one or more other substances. Non-limiting examples of other substances include diluents, salts, buffers, stabilizers, solubilizers, and preservatives. In certain embodiments, the other substance is a cyclodextrin, such as hydroxypropyl-β-cyclodextrin or sulfobutylether β-cyclodextrin.

A formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, sodium chloride, and water can be prepared by using any suitable technique, many of which are known to those skilled in the art. The formulation can be prepared in a batch or continuous process. Generally, the formulation can be prepared by combining the components thereof in any order. The term "component" as used herein includes individual ingredients (e.g., levothyroxine sodium, tromethamine, sodium iodide, sodium chloride, optional pH adjuster, etc.) as well as any combination of ingredients (e.g., levothyroxine sodium, tromethamine, sodium iodide, sodium chloride, optional pH adjuster, etc.). In some embodiments, the formulation is formed by combining the components together in a vessel. The components can be combined in any order.

In some embodiments, the water is added to a suitable vessel, then the tromethamine, sodium iodide, and sodium chloride are added, either sequentially or together, and the mixture is stirred. Next, the pH is adjusted to the desired value. Subsequently, the levothyroxine sodium is added, and the mixture is stirred until the levothyroxine sodium is dissolved. In some embodiments, the water and sodium chloride are combined and stirred until the sodium chloride is dissolved to provide an aqueous solution of sodium chloride. Subsequently, the levothyroxine sodium, tromethamine, and sodium iodide are added, either sequentially or together, and the mixture is stirred. Next, the pH is adjusted to the desired value. Optional ingredients, such as diluents, salts, buffers, stabilizers, solubilizers, and preservatives, can be provided to the formulation at any stage in its preparation.

In some embodiments, the formulation is filtered through one or more filters prior to filling the composition into one or more suitable containers, such as a vial, an ampoule, a cartridge, a syringe, or a bag. Preferably, one or more of the filtration steps and the filling step are performed under aseptic conditions in order to provide a sterile container comprising a sterile formulation. A sterile formulation of the invention is preferably one in which substantially all forms of microbial life have been destroyed by an appreciable amount to meet the sterilization criteria set forth in the U.S. Pharmacopeia. See U.S. Pharmacopeia 32, NF 27, 1 (2009) 80-86.

The invention also provides a container comprising a formulation comprising levothyroxine sodium, tromethamine, sodium iodide, sodium chloride, optional pH adjustor, and any other optional components. In certain embodiments, the container is a vial, an ampoule, a bag, a bottle, a cartridge, or a syringe. In some embodiments, the container, the composition, or both the container and the composition are sterile. Preferably, the container is sealed by way of a closure, such as a stopper, plunger, and/or tip-cap.

The container and closure can be made of glass, plastic, and/or rubber. One or more surfaces of the container and/or closure can be treated with a compound to limit reactivity with one or more components of the formulation. In some embodiments, the container and/or closure are treated with silicon. In other embodiments, the container is treated with ammonium sulfate ($(NH_4)_2SO_4$). The container can be clear or opaque, and can be any color. In some embodiments, the container is flint colored. In other embodiments, the container is amber colored.

In certain embodiments, the invention provides a prefilled syringe containing a formulation of the invention described herein. In certain embodiments, a syringe according to the invention is a component of an autoinjector.

In some embodiments, the liquid formulation of the invention contains not more than 1.5% liothyronine (T3). In other embodiments, the liquid formulation contains not more than 1.25% liothyronine, e.g., not more than 1.0% liothyronine, not more than 0.9% liothyronine, not more than 0.8% liothyronine, not more than 0.7% liothyronine, not more than 0.6% liothyronine, not more than 0.5% liothyronine, not more than 0.4% liothyronine, not more than 0.35% liothyronine, not more than 0.30% liothyronine, not more than 0.25% liothyronine, not more than 0.2% liothyronine, or any range therein. For example, in certain embodiments, the liquid formulation contains 0.2%-1.5% liothyronine, 0.25%-1.25% liothyronine, 0.25%-1.0% liothyronine, 0.3%-0.9% liothyronine, 0.2%-0.4% liothyronine, 0.25%-0.4% liothyronine, or 0.25%-0.35% liothyronine.

In some embodiments, the liquid formulation contains not more than a specified amount of liothyronine as measured after storage of the formulation at a predetermined temperature for a predetermined time period. In certain embodiments, the liquid formulation contains not more than 1.0% liothyronine, e.g., not more than 0.8% liothyronine, not more than 0.6% liothyronine, not more than 0.5% liothyronine, not more than 0.4% liothyronine, not more than 0.30% liothyronine, not more than 0.2% liothyronine, or any range therein as measured after storage of the formulation at 25±2° C. for a period of four months. In other embodiments, the

liquid formulation contains not more than 1.5% liothyronine, e.g., not more than 1.25%, not more than 1.0%, not more than 0.8%, not more than 0.6%, not more than 0.5%, not more than 0.4%, or any range therein as measured after storage of the formulation at 40±2° C. for a period of four months.

In some embodiments, the liquid formulation of the invention contains not more than 5.0% total impurities. In other embodiments, the liquid formulation contains not more than 4.0% total impurities, e.g., not more than 3.5% total impurities, not more than 3.0% total impurities, not more than 2.5% total impurities, not more than 2.0% total impurities, not more than 1.5% total impurities, not more than 1.25% total impurities, not more than 1.0% total impurities, not more than 0.9% total impurities, not more than 0.8% total impurities, not more than 0.7% total impurities, or any range therein. For example, in certain embodiments, the liquid formulation contains 1.0%-5.0% total impurities, 1.5%-3.5% total impurities, 0.8%-3.0% total impurities, 0.7%-2.0% total impurities, 1.25%-4.0% total impurities, 0.8%-1.5% total impurities, or 0.9%-1.25% total impurities.

In some embodiments, the liquid formulation contains not more than a specified amount of total impurities as measured after storage of the formulation at a predetermined temperature for a predetermined time period. In certain embodiments, the liquid formulation contains not more than 2.0% total impurities, e.g., not more than 1.5% total impurities, not more than 1.25% total impurities, not more than 1.0% total impurities, not more than 0.9% total impurities, not more than 0.8% total impurities, not more than 0.7% total impurities, or any range therein as measured after storage of the formulation at 25±2° C. for a period of four months. In other embodiments, the liquid formulation contains not more than 5.0% total impurities, e.g., not more than 4.0% total impurities, not more than 3.5% total impurities, not more than 3.0% total impurities, not more than 2.5% total impurities, not more than 2.0% total impurities, not more than 1.5% total impurities, or any range therein as measured after storage of the formulation at 40±2° C. for a period of four months.

The invention also provides a method of stabilizing a levothyroxine formulation by forming a mixture comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, sodium chloride, and water, thereby stabilizing the formulation. The identity and amounts of levothyroxine or pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, and sodium chloride present in the mixture as well as the pH can be the same as the identity and amounts of these components and the pH described herein with respect to a formulation of the invention. The formulation formed by the method of stabilizing a levothyroxine formulation can have the same stability characteristics as the stability characteristics described herein with respect to a formulation of the invention, particularly with regard to total impurities and liothyronine.

The formulation according to the invention is suitable for administration to a subject to treat or prevent a disease or condition. Preferably, the subject is a mammal. More preferably, the mammal is a human. Preferably, the disease or condition is a disease or condition that is treatable by the administration of levothyroxine or a pharmaceutically acceptable salt thereof, such as hypothyroidism. In some embodiments, the condition is myxedema coma.

The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

Example 1

This example demonstrates the stability of exemplary formulations comprising levothyroxine sodium, tromethamine, and water as a function of the pH of the formulation.

Separate samples containing levothyroxine sodium at a concentration of 20 mcg/mL, tromethamine at a concentration of 10 mg/mL in normal saline (0.9% NaCl in water) were adjusted to various pH levels. One sample additionally contained hydroxypropyl (HP) β-cyclodextrin at a concentration of 10 mg/mL. 5 mL of each sample was filled into 10 cc amber tubing vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at temperatures of 25° C., 40° C. and 55° C. The samples stored at 55° C. were analyzed by HPLC at 1 and 4 weeks (W) of storage. The samples stored at 40° C. were analyzed by HPLC at 4 W and 3 months (M) of storage. The samples stored at 25° C. were analyzed by HPLC at 3M of storage.

The HPLC conditions were as follows:

Column: Waters SYMMETRY™ C8 (5 μm, 4.6×150 mm) HPLC column

Mobile Phase A: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (4.023 g/800 mL/1600 mL/1600 mL/4 mL)

Mobile Phase B: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (2.013 g/1000 mL/100 mL/900 mL/2 mL)

Diluent: 0.01 N NaOH

Column temperature: 25° C.

Flow rate: 1.5 mL/min

Injection volume: 40-200 μL

Autosampler temperature: 5° C.

Detection: UV at 225 nm

Separation mode: Gradient

Gradient program:

Time	% Mobile Phase	
(minutes)	A	B
25	100	0
40	10	90
50	10	90
51	100	0
60	100	0

The relative response time (RRT) for liothyronine to levothyroxine was approximately 0.73.

The results for liothyronine, largest unknown impurity, and total impurities as determined by peak area percent are set forth in Table 1.

TABLE 1

	Levothyroxine Na (mcg/mL)			20		
	Tromethamine (mg/mL)			10		
	HP-β-cyclodextrin (mg/mL)	—	—	—	—	10
	Solvent			Normal saline		
	pH	8	9	9.5	10	9
55° C., 1 W	% Liothyronine	15.2	2.7	1.2	0.6	2.7
	% largest unknown impurity	1.59	0.67	0.50	0.27	0.86
	% total impurities	17.5	3.6	2.2	1.5	4.0

TABLE 1-continued

	Levothyroxine Na (mcg/mL)			20		
	Tromethamine (mg/mL)			10		
	HP-β-cyclodextrin (mg/mL)	—	—	—	—	10
	Solvent			Normal saline		
	pH	8	9	9.5	10	9
55° C., 4 W	% Liothyronine	nt	nt	1.7	3.1	nt
	% largest unknown impurity	nt	nt	0.09	0.55	nt
	% total impurities	nt	nt	2.1	4.2	nt
40° C., 4 W	% Liothyronine	nt	nt	0.9	0.4	nt
	% largest unknown impurity	nt	nt	0.12	0.12	nt
	% total impurities	nt	nt	1.7	0.6	nt
25° C., 3 M	% Liothyronine	nt	nt	0.6	0.35	nt
	% largest unknown impurity	nt	nt	0.46	0.11	nt
	% total impurities	nt	nt	1.51	0.71	nt
40° C., 3 M	% Liothyronine	nt	nt	1.56	0.87	nt
	% largest unknown impurity	nt	nt	0.48	0.16	nt
	% total impurities	nt	nt	2.66	1.35	nt

nt = not tested

The results described in Table 1 demonstrate reduced liothyronine and total impurities were detected in levothyroxine formulations having a pH of 9-10 as compared to pH 8.

The effect of pH on levothyroxine stability was further tested in samples having a pH 9.5-11.5. Separate samples containing levothyroxine sodium at a concentration of 20 mcg/mL or 100 mcg/mL, tromethamine at a concentration of 10 mg/mL in normal saline were adjusted to various pH levels. 5 mL of each sample was filled into 10 cc amber tubing vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at temperatures of 25° C., 40° C., and 55° C. The samples stored at 55° C. were analyzed by HPLC at 1 W and 2 W of storage. The samples stored at 25° C. and 40° C. were analyzed by HPLC at 2M of storage using the HPLC conditions described hereinabove.

The results for liothyronine, largest unknown impurity, and total impurities as determined by peak area percent are set forth in Table 2.

TABLE 2

	Levothyroxine Na (mcg/mL)	20	20	100	20
	Tromethamine (mg/mL)		10		
	Solvent		Normal saline		
	pH	9.5	10.4	10.4	11.5
55° C., 1 W	% Liothyronine	0.9	0.2	0.3	0.1
	% largest unknown impurity	0.09	0.09	0.11	0.08
	% total impurities	1.2	0.5	0.7	0.4
55° C., 2 W	% Liothyronine	1.9	0.4	0.8	0.2
	% largest unknown impurity	0.1	0.1	0.11	0.1
	% total impurities	2.0	0.9	1.1	0.4
25° C., 2 M	% Liothyronine	0.34	0.17	0.23	0.34
	% largest unknown impurity	0.11	0.20	0.11	15.4
	% total impurities	0.7	0.6	0.6	19.6
40° C., 2 M	% Liothyronine	1.00	0.38	0.49	0.31
	% largest unknown impurity	0.14	0.22	0.10	9.2
	% total impurities	1.44	0.88	0.8	12.1

The results described in Table 2 demonstrate that reduced liothyronine and/or total impurities were detected in levothyroxine formulations having a pH of 10.4 as compared to pH 9.5 or 11.5 following storage at 25° C. or 40° C. for 2M.

Example 2

This example demonstrates the stability of exemplary formulations comprising levothyroxine sodium, sodium iodide, and tromethamine as a function of sodium iodide concentration and pH of the formulation.

Separate samples containing 20 mcg/mL levothyroxine sodium, 10 mg/mL tromethamine, 5.4 mg/mL sodium chloride, and sodium iodide at a concentration of 280 mcg/mL, 140 mcg/mL, or 6 mcg/mL in water were adjusted to various pH levels. 5 mL of each sample was filled into 10 cc flint molded vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at temperatures of 25° C. or 55° C. for 4 W prior to analysis by HPLC.

The HPLC conditions were as follows:

Column: ACE Excel 3 C18-PFP, 4.6×150 mm HPLC column

Mobile Phase A: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (4.0 g/800 mL/1600 mL/1600 mL/4.0 mL)

Mobile Phase B: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (4.0 g/2000 mL/200 mL/1800 mL/4.0 mL)

Diluent: 0.01 N NaOH

Column temperature: 25° C.

Flow rate: 1.5 mL/min

Injection volume: 80 µL

Autosampler temperature: 5° C.

Detection: UV at 225 nm

Separation mode: Gradient

Gradient program:

Time	% Mobile Phase	
(minutes)	A	B
0	100	0
25	100	0
40	10	90
50	10	90
51	100	0
60	100	0

The relative response time (RRT) for liothyronine to levothyroxine was approximately 0.71.

The results for liothyronine, largest any other individual impurity (AOII), and total impurities as determined by peak area percent are set forth in Table 3.

TABLE 3

	Levothyroxine Na (mcg/mL)	20						
	Tromethamine (mg/mL)	10						
	Solvent	5.4 mg/mL sodium chloride in water						
	NaI (mcg/mL)	280			140			6
	pH	9.5	10	10.5	9.5	10	10.5	10.5
25° C., 4 W	% Liothyronine	0.28	0.26	0.26	0.28	0.27	0.26	0.25
	% AOII	0.56	0.55	0.57	0.52	0.55	0.6	0.33
	% total impurities	1.58	1.61	1.66	1.51	1.64	1.75	1.9
55° C., 4 W	% Liothyronine	1.63	1.06	0.71	1.74	1.06	0.74	0.87
	% AOII	0.53	0.54	0.53	0.59	0.61	0.53	0.99
	% total impurities	3.24	2.76	2.43	3.6	2.86	2.49	3.5

The samples also were stored at temperatures of 25° C. or 40° C. for 2M or 4M prior to analysis by HPLC.

The HPLC conditions were as follows:

Column: Phenomenex Kinetex 2.6 μm C18, 4.6×150 mm HPLC column
Mobile Phase A: 0.05 M Sulfamic Acid, pH 2.0
Mobile Phase B: Acetonitrile
Diluent: 10% Mobile Phase A in Methanol:Acetonitrile: Mobile Phase A (1000 mL:300 mL:700 mL)
Column temperature: 27° C.
Flow rate: 1.2 mL/min
Injection volume: 50 μL
Autosampler temperature: 25° C.
Detection: UV at 225 nm
Separation mode: Gradient
Gradient program:

Time	% Mobile Phase	
(minutes)	A	B
0	70	30
5	70	30
33	32	68
35	32	68
36	70	30
50	70	30

The relative response time (RRT) for liothyronine to levothyroxine was approximately 0.62.

The results for liothyronine, largest any other individual impurity (AOII), and total impurities as determined by peak area percent are set forth in Table 4.

TABLE 4

	Levothyroxine Na (mcg/mL)	20						
	Tromethamine (mg/mL)	10						
	Solvent	5.4 mg/mL sodium chloride in water						
	NaI (mcg/mL)	280			140			6
	pH	9.5	10	10.5	9.5	10	10.5	10.5
25° C., 2 M	% Liothyronine	0.28	0.24	0.23	0.29	0.25	0.24	0.26
	% AOII	0.11	0.12	0.11	0.09	0.10	0.12	0.46
	% total impurities	0.81	0.8	0.85	0.76	0.77	0.88	1.85
40° C., 2 M	% Liothyronine	0.9	0.55	0.39	0.88	0.55	0.41	0.43
	% AOII	0.13	0.13	0.17	0.14	0.14	0.15	0.91
	% total impurities	1.56	1.2	1.07	1.42	1.18	1.09	2.5
25° C., 4 M	% Liothyronine	0.35	0.28	0.25	0.35	0.28	0.26	0.25
	% AOII	2.14	0.17	0.11	0.18	0.17	0.17	1.21
	% total impurities	3.26	0.93	1.04	1.00	0.93	0.94	2.81
40° C., 4 M	% Liothyronine	1.23	0.84	0.58	1.3	0.86	0.59	0.6
	% AOII	0.52	1.38	1.07	0.72	0.92	0.69	1.45
	% total impurities	2.76	3.23	2.72	2.84	2.73	2.14	3.51

The results described in Tables 3 and 4 demonstrate that levels of liothyronine in formulations comprising 140 mcg/mL or 280 mcg/mL sodium iodide were decreased as the pH was increased from 9.5 to 10 and from 10 to 10.5 following storage at 55° C. for 4 W or at 40° C. for 2M or 4M. The levels of total impurities in formulations comprising 140 mcg/mL sodium iodide also were decreased as the pH was increased from 9.5 to 10 and from 10 to 10.5 following storage at 55° C. for 4 W or at 40° C. for 2M or 4M. Lower levels of AOII and total impurities were detected in formulations comprising 140 mcg/mL or 280 mcg/mL sodium iodide at pH 10.5 as compared to formulations comprising 6 mcg/mL sodium iodide at pH 10.5 following storage at 55° C.° for 4 W or at 40° C. for 2M or 4M.

Example 4

This example demonstrates the stability of exemplary formulations comprising levothyroxine sodium, sodium iodide, and tromethamine as a function of vial type.

An aqueous solution containing 20 mcg/mL levothyroxine sodium, 10 mg/mL tromethamine, 5.4 mg/mL sodium chloride, and 6 mcg/mL sodium iodide was adjusted to pH 10.5. 5 mL of the solution was filled into each of the vials described in Table 5, and the vials were stoppered under nitrogen.

TABLE 5

	Type	Size	Color	Glass vial preparation	Inner surface treatment
Vial 1	Glass	10 cc	Flint	Molded	No
Vial 2	Glass	10 cc	Amber	Molded	$(NH_4)_2SO_4$
Vial 3	Glass	5 cc	Amber	Tubing	$(NH_4)_2SO_4$
Vial 4	Glass	6 cc	Flint	Molded	No
Vial 5	Plastic[1]	10 cc	Opaque	N/A	N/A
Vial 6	Plastic[2]	10 cc	Opaque	N/A	N/A
Vial 7	Plastic[3]	10 cc	Clear	N/A	N/A
Vial 8	Plastic[3]	10 cc	Amber	N/A	N/A
Vial 9	Plastic[4]	10 cc	Clear	N/A	Silicon
Vial 10	Plastic[4]	10 cc	Amber	N/A	Silicon

[1]polypropylene copolymer - ExxonMobil PP9122
[2]polypropylene copolymer - Flint Hills Resources 23M2A
[3]cyclic olefin polymer - Daikyo CRYSTAL ZENITH™
[4]cyclic olefin polymer - SiO_2 Medical Products

The vials were stored at a temperature of 25° C. or 55° C. for 4 W prior to analysis by HPLC. The HPLC conditions were the same as described hereinabove for the data of Table 3. The results for liothyronine (T3), largest any other individual impurity (AOII), and total impurities as determined by peak area percent are set forth in Table 6.

TABLE 6

	Storage Temp					
	25° C.			55° C.		
Impurity	T3	AOII	Tot	T3	AOII	Tot
Vial 1	0.25	0.33	1.9	0.87	0.99	3.5
Vial 2	0.28	0.39	2	1.59	4.97	14.6
Vial 3	0.25	2.54	4.4	0.91	2.31	4.9
Vial 4	0.22	0.52	2.5	1.11	4.02	7.9
Vial 5	0.25	0.7	3.4	0.85	8.76	20.3
Vial 6	0.25	0.89	3.7	0.73	10.51	29.9
Vial 7	0.24	0.75	2.6	0.78	7.29	10.7
Vial 8	0.24	0.81	2.7	0.75	7.09	10.6
Vial 9	0.25	0.48	1.9	0.78	2.79	5.4
Vial 10	NT	NT	NT	0.76	3	5.7

The results described in Table 6 demonstrate that vial material, size, color, and/or treatment can affect the stability of formulations comprising levothyroxine sodium, sodium iodide, and tromethamine.

Example 5

This example demonstrates the stability of comparative formulations comprising levothyroxine sodium, glycerol, sodium chloride, and water as a function of the pH of the formulation.

Separate samples containing levothyroxine sodium at a concentration of 20 mcg/mL and glycerol at a concentration of 100 mg/mL in normal saline were adjusted to pH levels of 7, 8, and 9. 5 mL of each sample was filled into 10 cc amber tubing vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at a temperature of 55° C. The samples were analyzed by HPLC at 1 week of storage using the HPLC conditions described in Example 1. The results for liothyronine, largest unknown impurity, and total impurities as determined by peak area percent are set forth in Table 7.

TABLE 7

	Levothyroxine Na (mcg/mL)	20		
	Glycerol (mg/mL)	100		
	Solvent	Normal saline		
	pH	7	8	9
55° C., 1 W	% Liothyronine	3.6	3.4	2.4
	% largest unknown impurity	1.16	1.30	0.82
	% total impurities	5.3	5.4	3.8

The results described in Table 7 demonstrate that high levels of impurities are formed in levothyroxine formulations containing glycerol over the pH range 7-9 following storage at 55° C. for one week.

Example 6

This example demonstrates a method for preparing an exemplary formulation of the invention.

The composition of an exemplary formulation containing 100 mcg levothyroxine in 5 mL volume is as described in Table 8.

TABLE 8

Component	Quantity per mL
Levothyroxine sodium, USP	20 mcg
Sodium chloride	6.48 mg
Sodium iodide	0.14 mg
Tromethamine, USP	10 mg
Sodium hydroxide (1N)	As needed to adjust pH to 10-10.5
Hydrochloric acid (1N)	(target 10.3)
Purified water	q.s.

The compositions for exemplary formulations containing 200 mcg or 500 mcg levothyroxine in 5 mL volume are the same as described in Table 8, except that the concentrations of levothyroxine sodium are 40 mcg/mL and 100 mcg/mL, respectively.

An exemplary formulation is prepared by filling purified water in an amount of approximately 80% of a predetermined final batch volume into a suitable container. The entire amounts of sodium chloride, sodium iodide, and tromethamine are added in succession, with mixing until dissolution of each ingredient prior to addition of the next ingredient. The pH is determined, and then adjusted to pH 10.3 (range of 10.0 to 10.5) with sodium hydroxide and/or hydrochloric acid. The entire amount of levothyroxine sodium is added to the container, and the solution is mixed until dissolution. The pH is determined, and then adjusted to pH 10.3 (range of 10.0 to 10.5) with sodium hydroxide and/or hydrochloric acid. Purified water is added in an amount sufficient to reach the predetermined batch volume with continued mixing to ensure complete dissolution of all ingredients. The formulation can be bubbled with nitrogen or other suitable gas throughout the compounding to limit the dissolved oxygen in the formulation. Under aseptic conditions, the solution is filtered through a 0.22 μm filter, and then 5 mL of the filtered solution is filled into containers (e.g. vials) under nitrogen. The containers are then sealed (e.g., stoppered) under nitrogen.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term "at least one" followed by a list of one or more items (for example, "at least one of A and B") is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

The invention claimed is:

1. A liquid formulation comprising

levothyroxine or a pharmaceutically acceptable salt thereof;

a stabilizing agent comprising tromethamine;

not more than 2% liothyronine (T3); and

water;

wherein the formulation retains at least about 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for 12 months at 25±2° C., and retains at least about 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for 2 months at 40±2° C.

2. The formulation of claim **1**, wherein levothyroxine or a pharmaceutically acceptable salt thereof is levothyroxine sodium.

3. The formulation of claim **2**, wherein levothyroxine sodium is present at a concentration of from about 5 mcg/mL to about 500 mcg/mL.

4. The formulation of claim **1**, wherein the tromethamine is present at a concentration of about 1 mg/mL to about 50 mg/mL.

5. The formulation of claim **1**, wherein the stabilizing agent comprises a salt of iodine.

6. The formulation of claim **5**, wherein the salt of iodine is sodium iodide or potassium iodide.

7. The formulation of claim **6**, wherein the salt of iodine is sodium iodide which is present at a concentration of about 10 mcg/mL to about 500 mcg/mL.

8. The formulation of claim **1**, wherein the formulation has a pH of from about 9.0 to about 11.5.

9. The formulation of claim **8**, wherein the formulation has a pH of from about 9.8 to about 10.8.

10. The formulation of claim **1**, wherein the formulation contains not more than 1.5% liothyronine (T3).

11. The formulation of claim **1**, wherein the formulation contains not more than 1.0% liothyronine (T3).

12. The formulation of claim **1**, wherein the formulation contains not more than 5.0% total impurities.

13. The formulation of claim **1**, wherein the formulation contains not more than 2.5% total impurities.

14. The formulation of claim **1**, wherein the formulation retains at least about 90% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for at least 18 months at 25±2° C.

15. The formulation of claim **1**, wherein the formulation retains at least about 90% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for at least 24 months at 25±2° C.

16. The formulation of claim **1**, wherein the formulation does not contain a buffer.

17. The formulation of claim **1**, wherein the formulation is a ready-to-use formulation contained within a vial, ampoule, cartridge, syringe, or bag.

* * * * *

EXHIBIT B

US011135190B2

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

(10) **Patent No.: US 11,135,190 B2**
(45) **Date of Patent: *Oct. 5, 2021**

(54) **LEVOTHYROXINE LIQUID FORMULATIONS**

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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. 15/700,258, filed on Sep. 11, 2017, now Pat. No. 10,398,669, which is a continuation of application No. 15/366,864, filed on Dec. 1, 2016, now Pat. No. 9,782,376.

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A61K 47/02	(2006.01)
A61K 9/00	(2006.01)
A61K 33/18	(2006.01)

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

CPC ***A61K 31/198*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 33/18*** (2013.01); ***A61K 47/02*** (2013.01); ***A61K 47/18*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/33

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,035,974	A	5/1962	Israel
5,951,989	A	9/1999	Heymann
6,383,471	B1	5/2002	Chen et al.
6,458,842	B1	10/2002	Dickinson et al.
6,645,526	B2	11/2003	Hanshew, Jr. et al.
6,706,255	B2	3/2004	Dickinson et al.
6,936,274	B2	8/2005	Hanshew, Jr. et al.
7,052,717	B2	5/2006	Hanshew, Jr. et al.
7,195,779	B2	3/2007	Hanshew, Jr. et al.
7,723,390	B2	5/2010	Garavani et al.
7,858,663	B1	12/2010	Bristol et al.
8,318,712	B2	11/2012	Pierres et al.
8,759,572	B2	6/2014	Viscardi et al.
8,779,000	B1	7/2014	Parikh et al.
9,006,289	B2	4/2015	Jiang et al.
9,050,307	B2	6/2015	Psarrakis et al.
9,168,238	B2	10/2015	Jiang et al.
9,168,239	B2	10/2015	Jiang et al.
9,345,772	B1	5/2016	Parikh et al.
9,428,444	B2	8/2016	Rao et al.
9,782,376	B1	10/2017	Usayapant et al.
2005/0059574	A1	3/2005	Klein et al.
2009/0270507	A1	10/2009	Pierres et al.
2016/0331711	A1	11/2016	Parikh et al.
2017/0319526	A1	11/2017	Tengler
2018/0064669	A1	3/2018	Tengler
2018/0153838	A1	6/2018	Usayapant et al.
2018/0214374	A1	8/2018	Chandrashekhar et al.
2019/0060217	A1	2/2019	Chandrashekhar et al.

FOREIGN PATENT DOCUMENTS

WO	2015/151013	A1	10/2015
WO	2017/013591	A1	1/2017
WO	2017/077476	A1	5/2017
WO	2019/023791	A1	2/2019
WO	2019/094292	A1	5/2019

OTHER PUBLICATIONS

U.S. Appl. No. 15/366,864, filed Dec. 1, 2016.

U.S. Appl. No. 15/700,258, filed Sep. 11, 2017.

Bernareggi et al., "Oral Liquid Formulation of Levothyroxine is Stable in Breakfast Beverages and May Improve Thyroid Patient Compliance," *Pharmaceutics*, 5: 621-633 (2013).

Collier et al., "Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate," *AAPS PharmSciTech*, 11(2): 818-825 (2010).

Kannamkumarath et al., "Determination of Levothyroxine and its Degradation Products in Pharmaceutical Tablets by HPLC-UV-ICP-MS," *J. Anal. At. Spectrom.*, 19: 107-113 (2004).

Kazemifard et al., "Identification and Quantitation of Sodium-Thyroxine and its Degradation Products by LC Using Electrochemical and MS Detection," *J. Pharm. Biomed. Anal.*, 25: 697-711 (2001).

Patel, "The Effect of Formulation and Processing Variables on the Stability of Levothyroxine Sodium Tablets," Dissertation submitted to Univ. Cincinnati Coll. of Pharmacy: pp. 1-151 (May 2003).

Patel et al., "The Effect of Excipients on the Stability of Levothyroxine Sodium Pentahydrate Tablets," *Int. J. Pharm.*, 264: 35-43 (2003).

Remington Pharmaceutical Science, 17th Edition, Alfonso R. Gennaro, Editor, Mack Publishing Company, Easton, PA, USA, pp. 836-837, 1455-1472 (1985).

Schering Corp., Prescribing Information for LEVENTA Levothyroxine Sodium Solution: pp. 1-5 (Oct. 2010).

(Continued)

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(57) **ABSTRACT**

The present invention is directed to a pharmaceutical product which includes a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof. The formulation of the present invention includes tromethamine, sodium iodide, and water and has a pH of about 9.0 to about 11.5. The liquid formulation according to the invention is stable and ready-to-use.

16 Claims, No Drawings

(56) **References Cited**

OTHER PUBLICATIONS

Shah et al., "Stability Indication Validated HPLC Method for Quantification of Levothyroxine with Eight Degradation Peaks in the Presence of Excipients," *Int. J. Pharm.*, 360: 77-82 (2008).
Stadalman et al., "Stability of Levothyroxine Sodium 0.4 µg/mL in 0.9% Sodium Chloride Injection," *Prog. Transplant.*, 19(4): 354-356 (2009).
Strong et al., "Stability of Levothyroxine in Sodium Chloride for IV Administration," *Can. J. Hosp. Pharm.*, 63(6): 437-443 (2010).
United States Pharmacopeial Convention, "Levothyroxine Sodium," United States Pharmacopeia and National Formulary (Revision Bulletin): pp. 1-3 (Oct. 2010).
Won, "Kinetics and Degradation of Levothyroxine in Aqueous Solution and in Solid State," *Pharm. Res.*, 9(1): 131-137 (1992).
Pramanick et al., "Excipient Selection in Parenteral Formulation Development," *Pharma Times* 45(3): 65-77 (2013).
European Patent Office, International Search Report in International Application No. PCT/US2017/062019 (dated Feb. 21, 2018).
European Patent Office, Written Opinion in International Application No. PCT/US2017/062019 (dated Feb. 21, 2018).

LEVOTHYROXINE LIQUID FORMULATIONS

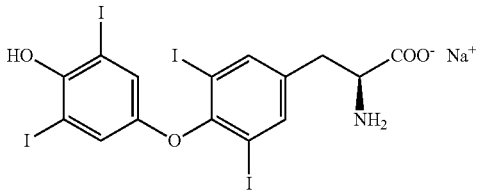
CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a continuation of U.S. patent application Ser. No. 15/700,258, filed Sep. 11, 2017, now U.S. Pat. No. 10,398,669, which is a continuation of U.S. patent application Ser. No. 15/366,864, filed Dec. 1, 2016, now U.S. Pat. No. 9,782,376, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

BACKGROUND OF THE INVENTION

Levothyroxine sodium for injection is a sterile lyophilized product for parenteral administration of levothyroxine sodium for thyroid replacement therapy. Levothyroxine sodium for injection is particularly useful when thyroid replacement is needed on an urgent basis, for short term thyroid replacement, and/or when oral administration is not possible, such as for a patient in a state of myxedema coma.

Full chemical names for levothyroxine sodium include 4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodo-L-phenylalanine sodium, and L-tyrosine-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-monosodium salt. Levothyroxine sodium has a molecular weight of approximately 798.85 and the following chemical structure:



Conventional formulations of levothyroxine sodium for injection are preservative-free lyophilized powders containing levothyroxine sodium and the excipients mannitol, sodium phosphate buffer, and sodium hydroxide. Administration of the conventional formulations involve reconstitution of the lyophilized powder in 0.9% sodium chloride injection (USP) to provide an injectable solution.

However, use of the conventional lyophilized formulations requires reconstitution or dilution by healthcare practitioners prior to use. Once reconstituted, the levothyroxine sodium solutions have a limited stability, and must be used within a few hours of reconstitution. In addition, contaminants may be introduced into the solutions during the reconstitution process, thereby compromising patient safety.

It has been shown that levothyroxine in oral tablets and in aqueous solutions undergoes degradation. Major degradation products of levothyroxine are known to include 3,3',5-triiodothyronine (T3) 3,5-diiodothyronine (T2) 3,3',5,5'-tetraiodothyroacetic acid (TTAA4) 3,3',5-triiodothyroacetic acid (TTAA3) and 3,5-diiodothyroacetic acid (TTAA2) (Kannamkumarath et al., *J. Anal. At. Spectrom.,* 2004, 19: 107-113 and Patel et al., *Int. J. Pharm.,* 2003, 264: 35-43)). 3,3',5-triiodothyronine, known as liothyronine or T3, is a major degradant. Aqueous solutions of levothyroxine sodium have been shown to be more stable at basic pH than at acidic pH, but significant degradation of levothyroxine sodium also has been shown to occur at basic pH (Patel et al., *Int. J. Pharm.,* 2003, 264: 35-43).

Thus, there remains a need in the art for a ready-to-use injectable formulation of levothyroxine sodium that exhibits storage stability.

BRIEF SUMMARY OF THE INVENTION

The invention provides a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, and water, wherein the formulation has a pH of about 9.0 to about 11.5.

The invention also provides a liquid formulation comprising (a) levothyroxine or a pharmaceutically acceptable salt thereof in a concentration of about 20 mcg/mL to about 100 mcg/mL, (b) tromethamine in a concentration of about 5 mg/mL to about 20 mg/mL, (c) sodium iodide in a concentration of about 100 mcg/mL to about 300 mcg/mL, (d) sodium chloride, and (e) water, wherein the formulation has a pH of about 9.8 to about 10.8.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, and water, wherein the formulation has a pH of about 9.0 to about 11.5. The liquid formulation according to the invention is stable and ready-to-use.

As used herein, a "ready-to-use" formulation is a sterile, injectable formulation that is not reconstituted from a solid by a healthcare provider prior to use. Rather, a ready-to-use formulation is supplied by a pharmaceutical manufacturer in a suitable container (e.g., vial, syringe, bag, container) in liquid form. In some embodiments, a ready-to-use formulation is an injectable formulation that is administered to a subject without dilution. In other embodiments, a ready-to-use formulation is a concentrated, liquid solution that must be diluted prior to administration to a subject. Thus, in some embodiments, the formulation of the present invention can be further diluted in an appropriate diluent such as, for example, WFI (water for injection), 0.9% sodium chloride, or 5% dextrose to a lower levothyroxine concentration.

The formulation according to the present invention is stable. As used herein, the terms "stable" and "stability" encompass any characteristic of the formulation which may be affected by storage conditions including, without limitation, potency, total impurities, levothyroxine degradation products, specific optical rotation, optical purity, water content, appearance, viscosity, sterility, and color and clarity. The storage conditions which may affect stability include, for example, duration of storage, temperature, humidity, and/or light exposure.

In certain embodiments, a stable levothyroxine formulation refers to a formulation that retains at least about 90%, or about least about 95%, or at least about 96%, or at least about 98%, of the labeled concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage under typical and/or accelerated conditions. In further embodiments, a stable levothyroxine formulation refers to less than about 15% (area percent), or less than about 10% (area percent), or less than about 7% (area percent), or less than about 5% (area percent), or less than about 2% (area percent) of levothyroxine-related impurities are present after storage under typical and/or accelerated conditions.

In some embodiments, the liquid formulation of the invention is stable for at least 12 months, at least 18 months, at least 24 months, or at least 36 months at refrigerated temperature (e.g., at 5±2° C.). In other embodiments, the liquid formulation of the invention is stable for at least 12 months, at least 18 months, at least 24 months, or at least 36 months at room temperature (e.g., at 25±2° C.).

Methods for determining the stability of a formulation of the invention with respect to a given parameter are well-known to those of skill in the art. For example, individual impurities and total impurities can be assessed by high-performance liquid chromatography (HPLC) or thin layer chromatography (TLC). Unless otherwise indicated to the contrary, a percentage amount of liothyronine, other individual impurities, or total impurities reported herein in the formulation is determined by a peak area percent method using HPLC.

The formulation comprises levothyroxine or any pharmaceutically acceptable salt thereof. Preferably, the formulation comprises levothyroxine sodium. In an embodiment, the levothyroxine sodium is levothyroxine sodium pentahydrate, which is the sodium salt of the levo-isomer of thyroxine, an active physiological substance found in the thyroid gland.

When the formulation comprises levothyroxine sodium, the levothyroxine sodium can be present in the formulation in any suitable concentration. Typically, levothyroxine sodium can be present in the formulation at a concentration of about 5 mcg/mL (micrograms/milliliter) or more, for example, about 10 mcg/mL or more, about 15 mcg/mL or more, about 20 mcg/mL or more, about 25 mcg/mL or more, about 30 mcg/mL or more, about 35 mcg/mL or more, about 40 mcg/mL or more, or about 45 mcg/mL or more.

Alternatively, levothyroxine sodium can be present in the formulation at a concentration of about 500 mcg/mL or less, for example, about 450 mcg/mL or less, about 400 mcg/mL or less, about 350 mcg/mL or less, about 300 mcg/mL or less, about 250 mcg/mL or less, about 200 mcg/mL or less, or about 150 mcg/mL or less.

Levothyroxine sodium can be present in the formulation in a concentration bounded by any two of the aforementioned endpoints. For example, levothyroxine sodium can be present in the formulation in a concentration of about 5 mcg/mL to about 500 mcg/mL, for example, about 10 mcg/mL to about 450 mcg/mL, about 15 mcg/mL to about 400 mcg/mL, about 20 mcg/mL to about 350 mcg/mL, about 25 mcg/mL to about 300 mcg/mL, about 30 mcg/mL to about 300 mcg/mL, about 35 mcg/mL to about 300 mcg/mL, about 40 mcg/mL to about 300 mcg/mL, about 45 mcg/mL to about 300 mcg/mL, or about 50 mcg/mL to about 250 mcg/mL, or about 20 mcg/mL to about 100 mcg/mL.

In a preferred embodiment, levothyroxine sodium is present at a concentration of about 20 mcg/mL. In another preferred embodiment, levothyroxine sodium is present at a concentration of about 40 mcg/mL. In yet another preferred embodiment, levothyroxine sodium is present at a concentration of about 100 mcg/mL.

The formulation can be provided in any suitable volume. In some embodiments, the volume of the formulation is about 0.5 mL or more, e.g., about 1 mL or more, about 3 mL or more, about 5 mL or more, about 8 mL or more, about 10 mL or more, about 20 mL or more, or about 50 mL or more. In other embodiments, the volume of the formulation is about 200 mL or less, e.g., about 150 mL or less, about 100 mL or less, about 50 mL or less, about 30 mL or less, about 15 mL or less, about 10 mL or less, or about 5 mL or less. The formulation can be provided in a volume bounded by any two of the aforementioned endpoints. For example, the formulation can be provided in a volume of about 1 mL to about 200 mL, about 1 mL to about 50 mL, about 3 mL to about 30 mL, about 5 mL to about 100 mL, or about 3 mL to about 10 mL. In certain preferred embodiments, the volume of the formulation is about 5 mL. One of ordinary skill in the art can readily select an appropriate container based upon the volume of the formulation.

The formulation comprises at least one stabilizing agent. The stabilizing agent serves to stabilize levothyroxine or a pharmaceutically acceptable salt thereof in the liquid formulation.

In some embodiments, the stabilizing agent is an amine. Non-limiting examples of suitable amines include trometh-amine (i.e., 2-amino-2-hydroxymethyl-propane-1,3-diol or Tris), bis(2-hydroxyethyl)-imino-tris(hydroxymethyl)meth-ane (Bis-tris or Bis-tris methane), monoethanolamine, diethanolamine, triethanolamine, 2-amino-2-methyl-1,3-propanediol, 2-dimethylamino-2-methyl-1-propanediol, 2-amino-2-ethylpropanol, 2-amino-1-butanol, and 2-amino-2-methyl-1-propanol. Preferably, the amine is trometh-amine.

The amine can be present in the formulation in any suitable concentration. Typically, the amine can be present in the formulation at a concentration of about 1 mg/mL (mil-ligram/milliliter) or more, for example, about 5 mg/mL or more, about 10 mg/mL or more, about 15 mg/mL or more, or about 20 mg/mL or more. Alternatively, the amine can be present in the formulation at a concentration of about 50 mg/mL or less, for example, about 45 mg/mL or less, about 40 mg/mL or less, about 35 mg/mL or less, about 30 mg/mL or less, about 25 mg/mL or less, or about 20 mg/mL or less.

Thus, the amine can be present in the formulation in a concentration bounded by any two of the aforementioned endpoints. For example, the amine can be present in the formulation in a concentration of about 1 mg/mL to about 50 mg/mL, for example, about 1 mg/mL to about 50 mg/mL, about 5 mg/mL to about 45 mg/mL, about 5 mg/mL to about 40 mg/mL, about 5 mg/mL to about 35 mg/mL, about 5 mg/mL to about 30 mg/mL, about 5 mg/mL to about 25 mg/mL, or about 5 mg/mL to about 20 mg/mL. In a preferred embodiment, the amine is tromethamine present at a concentration of about 20 mg/mL. In another preferred embodiment, the amine is tromethamine present at a concentration of about 10 mg/mL.

In some embodiments, the stabilizing agent is a salt of iodine, such as sodium iodide or potassium iodide. In some embodiments, the formulation comprises sodium iodide at a concentration of about 10 mcg/mL or more, e.g., 25 mcg/mL or more, 50 mcg/mL or more, 75 mcg/mL or more, 100 mcg/mL or more, 125 mcg/mL or more, 150 mcg/mL or more, 175 mcg/mL or more, or 200 mcg/mL or more. In other embodiments, the formulation comprises sodium iodide at a concentration of about 500 mcg/mL or less, e.g., 450 mcg/mL or less, 400 mcg/mL or less, 350 mcg/mL or less, 300 mcg/mL or less, 250 mcg/mL or less, 200 mcg/mL or less, 175 mcg/mL or less, or 150 mcg/mL or less.

Thus, the sodium iodide can be present in the formulation in a concentration bounded by any two of the aforementioned endpoints. For example, the sodium iodide can be present in the formulation in a concentration of about 10 mcg/mL to about 500 mcg/mL, for example, about 50 mcg/mL to about 400 mcg/mL, about 100 mcg/mL to about 300 mcg/mL, about 125 mcg/mL to about 300 mcg/mL, about 125 mcg/mL to about 250 mcg/mL, about 125 mcg/mL to about 200 mcg/mL, about 125 mcg/mL to about 175 mcg/mL, or about 125 mcg/mL to about 150 mcg/mL. In a

preferred embodiment, the sodium iodide is present at a concentration of about 140 mcg/mL.

The formulation can comprise one, two, or three or more stabilizing agents. In certain embodiments, the formulation comprises an amine and a salt of iodine, preferably tromethamine and sodium iodide. In some embodiments, the formulation comprises about 10 mg/mL tromethamine and about 140 mcg/mL sodium iodide.

The formulation comprises an isotonicity adjuster. Non-limiting examples of suitable isotonicity adjusters include sodium chloride, potassium chloride, dextrose, glycerin, and mannitol. In a preferred embodiment, the isotonicity adjuster is sodium chloride.

The isotonicity adjuster can be present at any suitable concentration. In some embodiments, the isotonicity adjuster is present at a concentration that renders the formulation isotonic or approximately isotonic with cells (e.g., red blood cells) and/or isotonic or approximately isotonic to blood plasma.

The formulation optionally comprises a pH adjuster. The pH adjuster can be any suitable pH adjuster, for example, the pH adjuster can be sodium hydroxide, potassium hydroxide, hydrochloric acid, or combinations thereof. In a preferred embodiment, the pH adjuster is sodium hydroxide, hydrochloric acid, or a combination thereof.

The formulation can have any suitable pH. Typically, the formulation can have a pH of about 9.0 or more including, for example, about 9.0 or more, about 9.2 or more, about 9.4 or more, about 9.6 or more, about 9.8 or more, about 10.0 or more, or about 10.2 or more. Alternatively, the formulation can have a pH of about 11.5 or less including, for example, about 11.3 or less, about 11.1 or less, about 11.0 or less, about 10.9 or less, about 10.8 or less, about 10.7 or less, about 10.6 or less, or about 10.5 or less.

The formulation can have a pH bounded by any two of the above endpoints recited for the formulation. For example the formulation can have a pH of about 9.0 to about 11.5 including, for example, about 9.0 to about 11.0, about 9.2 to about 10.8, about 9.2 to about 10.8, about 9.4 to about 10.8, about 9.6 to about 10.8, about 9.8 to about 10.8, about 10.0 to about 10.8, about 10.0 to about 10.7, about 10.0 to about 10.5, or about 10.2 to about 10.6.

Tromethamine has a buffering range of about 7 to about 9. In a preferred embodiment, the pH of the formulation is about 9.8 to about 10.8, which is above the buffering range of tromethamine. While not wishing to be bound by any particular theory, it is believed that tromethamine exerts a stabilizing effect on levothyroxine by a mechanism unrelated to buffering of the formulation.

In a preferred embodiment, the formulation comprises (a) levothyroxine or a pharmaceutically acceptable salt thereof in a concentration of about 20 mcg/mL to about 100 mcg/mL, (b) tromethamine in a concentration of about 5 mg/mL to about 20 mg/mL, (c) sodium iodide in a concentration of about 100 mcg/mL to about 300 mcg/mL, (d) sodium chloride, and (e) water, wherein the formulation has a pH of about 9.8 to about 10.8.

The formulation that comprises levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, sodium chloride, and water may further include one or more other substances. Non-limiting examples of other substances include diluents, salts, buffers, stabilizers, solubilizers, and preservatives. In certain embodiments, the other substance is a cyclodextrin, such as hydroxypropyl-β-cyclodextrin or sulfobutylether β-cyclodextrin.

A formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, sodium chloride, and water can be prepared by using any suitable technique, many of which are known to those skilled in the art. The formulation can be prepared in a batch or continuous process. Generally, the formulation can be prepared by combining the components thereof in any order. The term "component" as used herein includes individual ingredients (e.g., levothyroxine sodium, tromethamine, sodium iodide, sodium chloride, optional pH adjuster, etc.) as well as any combination of ingredients (e.g., levothyroxine sodium, tromethamine, sodium iodide, sodium chloride, optional pH adjuster, etc.). In some embodiments, the formulation is formed by combining the components together in a vessel. The components can be combined in any order.

In some embodiments, the water is added to a suitable vessel, then the tromethamine, sodium iodide, and sodium chloride are added, either sequentially or together, and the mixture is stirred. Next, the pH is adjusted to the desired value. Subsequently, the levothyroxine sodium is added, and the mixture is stirred until the levothyroxine sodium is dissolved. In some embodiments, the water and sodium chloride are combined and stirred until the sodium chloride is dissolved to provide an aqueous solution of sodium chloride. Subsequently, the levothyroxine sodium, tromethamine, and sodium iodide are added, either sequentially or together, and the mixture is stirred. Next, the pH is adjusted to the desired value. Optional ingredients, such as diluents, salts, buffers, stabilizers, solubilizers, and preservatives, can be provided to the formulation at any stage in its preparation.

In some embodiments, the formulation is filtered through one or more filters prior to filling the composition into one or more suitable containers, such as a vial, an ampoule, a cartridge, a syringe, or a bag. Preferably, one or more of the filtration steps and the filling step are performed under aseptic conditions in order to provide a sterile container comprising a sterile formulation. A sterile formulation of the invention is preferably one in which substantially all forms of microbial life have been destroyed by an appreciable amount to meet the sterilization criteria set forth in the U.S. Pharmacopeia. See U.S. Pharmacopeia 32, NF 27, 1 (2009) 80-86.

The invention also provides a container comprising a formulation comprising levothyroxine sodium, tromethamine, sodium iodide, sodium chloride, optional pH adjustor, and any other optional components. In certain embodiments, the container is a vial, an ampoule, a bag, a bottle, a cartridge, or a syringe. In some embodiments, the container, the composition, or both the container and the composition are sterile. Preferably, the container is sealed by way of a closure, such as a stopper, plunger, and/or tip-cap.

The container and closure can be made of glass, plastic, and/or rubber. One or more surfaces of the container and/or closure can be treated with a compound to limit reactivity with one or more components of the formulation. In some embodiments, the container and/or closure are treated with silicon. In other embodiments, the container is treated with ammonium sulfate ($(NH_4)_2SO_4$). The container can be clear or opaque, and can be any color. In some embodiments, the container is flint colored. In other embodiments, the container is amber colored.

In certain embodiments, the invention provides a prefilled syringe containing a formulation of the invention described herein. In certain embodiments, a syringe according to the invention is a component of an autoinjector.

In some embodiments, the liquid formulation of the invention contains not more than 1.5% liothyronine (T3). In other embodiments, the liquid formulation contains not more than 1.25% liothyronine, e.g., not more than 1.0%

liothyronine, not more than 0.9% liothyronine, not more than 0.8% liothyronine, not more than 0.7% liothyronine, not more than 0.6% liothyronine, not more than 0.5% liothyronine, not more than 0.4% liothyronine, not more than 0.35% liothyronine, not more than 0.30% liothyronine, not more than 0.25% liothyronine, not more than 0.2% liothyronine, or any range therein. For example, in certain embodiments, the liquid formulation contains 0.2%-1.5% liothyronine, 0.25%-1.25% liothyronine, 0.25%-1.0% liothyronine, 0.3%-0.9% liothyronine, 0.2%-0.4% liothyronine, 0.25%-0.4% liothyronine, or 0.25%-0.35% liothyronine.

In some embodiments, the liquid formulation contains not more than a specified amount of liothyronine as measured after storage of the formulation at a predetermined temperature for a predetermined time period. In certain embodiments, the liquid formulation contains not more than 1.0% liothyronine, e.g., not more than 0.8% liothyronine, not more than 0.6% liothyronine, not more than 0.5% liothyronine, not more than 0.4% liothyronine, not more than 0.30% liothyronine, not more than 0.2% liothyronine, or any range therein as measured after storage of the formulation at 25±2° C. for a period of four months. In other embodiments, the liquid formulation contains not more than 1.5% liothyronine, e.g., not more than 1.25%, not more than 1.0%, not more than 0.8%, not more than 0.6%, not more than 0.5%, not more than 0.4%, or any range therein as measured after storage of the formulation at 40±2° C. for a period of four months.

In some embodiments, the liquid formulation of the invention contains not more than 5.0% total impurities. In other embodiments, the liquid formulation contains not more than 4.0% total impurities, e.g., not more than 3.5% total impurities, not more than 3.0% total impurities, not more than 2.5% total impurities, not more than 2.0% total impurities, not more than 1.5% total impurities, not more than 1.25% total impurities, not more than 1.0% total impurities, not more than 0.9% total impurities, not more than 0.8% total impurities, not more than 0.7% total impurities, or any range therein. For example, in certain embodiments, the liquid formulation contains 1.0%-5.0% total impurities, 1.5%-3.5% total impurities, 0.8%-3.0% total impurities, 0.7%-2.0% total impurities, 1.25%-4.0% total impurities, 0.8%-1.5% total impurities, or 0.9%-1.25% total impurities.

In some embodiments, the liquid formulation contains not more than a specified amount of total impurities as measured after storage of the formulation at a predetermined temperature for a predetermined time period. In certain embodiments, the liquid formulation contains not more than 2.0% total impurities, e.g., not more than 1.5% total impurities, not more than 1.25% total impurities, not more than 1.0% total impurities, not more than 0.9% total impurities, not more than 0.8% total impurities, not more than 0.7% total impurities, or any range therein as measured after storage of the formulation at 25±2° C. for a period of four months. In other embodiments, the liquid formulation contains not more than 5.0% total impurities, e.g., not more than 4.0% total impurities, not more than 3.5% total impurities, not more than 3.0% total impurities, not more than 2.5% total impurities, not more than 2.0% total impurities, not more than 1.5% total impurities, or any range therein as measured after storage of the formulation at 40±2° C. for a period of four months.

The invention also provides a method of stabilizing a levothyroxine formulation by forming a mixture comprising levothyroxine or a pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, sodium chloride, and water, thereby stabilizing the formulation. The identity and amounts of levothyroxine or pharmaceutically acceptable salt thereof, tromethamine, sodium iodide, and sodium chloride present in the mixture as well as the pH can be the same as the identity and amounts of these components and the pH described herein with respect to a formulation of the invention. The formulation formed by the method of stabilizing a levothyroxine formulation can have the same stability characteristics as the stability characteristics described herein with respect to a formulation of the invention, particularly with regard to total impurities and liothyronine.

The formulation according to the invention is suitable for administration to a subject to treat or prevent a disease or condition. Preferably, the subject is a mammal. More preferably, the mammal is a human. Preferably, the disease or condition is a disease or condition that is treatable by the administration of levothyroxine or a pharmaceutically acceptable salt thereof, such as hypothyroidism. In some embodiments, the condition is myxedema coma.

The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

Example 1

This example demonstrates the stability of exemplary formulations comprising levothyroxine sodium, tromethamine, and water as a function of the pH of the formulation.

Separate samples containing levothyroxine sodium at a concentration of 20 mcg/mL, tromethamine at a concentration of 10 mg/mL in normal saline (0.9% NaCl in water) were adjusted to various pH levels. One sample additionally contained hydroxypropyl (HP) β-cyclodextrin at a concentration of 10 mg/mL. 5 mL of each sample was filled into 10 cc amber tubing vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at temperatures of 25° C., 40° C. and 55° C. The samples stored at 55° C. were analyzed by HPLC at 1 and 4 weeks (W) of storage. The samples stored at 40° C. were analyzed by HPLC at 4 W and 3 months (M) of storage. The samples stored at 25° C. were analyzed by HPLC at 3M of storage.

The HPLC conditions were as follows:

Column: Waters SYMMETRY™ C8 (5 μm, 4.6×150 mm) HPLC column

Mobile Phase A: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (4.023 g/800 mL/1600 mL/1600 mL/4 mL)

Mobile Phase B: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (2.013 g/1000 mL/100 mL/900 mL/2 mL)

Diluent: 0.01 N NaOH

Column temperature: 25° C.

Flow rate: 1.5 mL/min

Injection volume: 40-200 μL

Autosampler temperature: 5° C.

Detection: UV at 225 nm

Separation mode: Gradient

Gradient program:

Time	% Mobile Phase	
(minutes)	A	B
25	100	0
40	10	90

-continued

Time (minutes)	% Mobile Phase A	% Mobile Phase B
50	10	90
51	100	0
60	100	0

The relative response time (RRT) for liothyronine to levothyroxine was approximately 0.73.

The results for liothyronine, largest unknown impurity, and total impurities as determined by peak area percent are set forth in Table 1.

TABLE 1

	Levothyroxine Na (mcg/mL)	20				
	Tromethamine (mg/mL)	10				
	HP-β-cyclodextrin (mg/mL)	—	—	—	—	10
	Solvent	Normal saline				
	pH	8	9	9.5	10	9
55° C., 1 W	% Liothyronine	15.2	2.7	1.2	0.6	2.7
	% largest unknown impurity	1.59	0.67	0.50	0.27	0.86
	% total impurities	17.5	3.6	2.2	1.5	4.0
55° C., 4 W	% Liothyronine	nt	nt	1.7	3.1	nt
	% largest unknown impurity	nt	nt	0.09	0.55	nt
	% total impurities	nt	nt	2.1	4.2	nt
40° C., 4 W	% Liothyronine	nt	nt	0.9	0.4	nt
	% largest unknown impurity	nt	nt	0.12	0.12	nt
	% total impurities	nt	nt	1.7	0.6	nt
25° C., 3 M	% Liothyronine	nt	nt	0.6	0.35	nt
	% largest unknown impurity	nt	nt	0.46	0.11	nt
	% total impurities	nt	nt	1.51	0.71	nt
40° C., 3 M	% Liothyronine	nt	nt	1.56	0.87	nt
	% largest unknown impurity	nt	nt	0.48	0.16	nt
	% total impurities	nt	nt	2.66	1.35	nt

nt = not tested

The results described in Table 1 demonstrate reduced liothyronine and total impurities were detected in levothyroxine formulations having a pH of 9-10 as compared to pH 8.

The effect of pH on levothyroxine stability was further tested in samples having a pH 9.5-11.5. Separate samples containing levothyroxine sodium at a concentration of 20 mcg/mL or 100 mcg/mL, tromethamine at a concentration of 10 mg/mL in normal saline were adjusted to various pH levels. 5 mL of each sample was filled into 10 cc amber tubing vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at temperatures of 25° C., 40° C., and 55° C. The samples stored at 55° C. were analyzed by HPLC at 1 W and 2 W of storage. The samples stored at 25° C. and 40° C. were analyzed by HPLC at 2M of storage using the HPLC conditions described hereinabove.

The results for liothyronine, largest unknown impurity, and total impurities as determined by peak area percent are set forth in Table 2.

TABLE 2

	Levothyroxine Na (mcg/mL)	20	20	100	20
	Tromethamine (mg/mL)	10			
	Solvent	Normal saline			
	pH	9.5	10.4	10.4	11.5
55° C., 1 W	% Liothyronine	0.9	0.2	0.3	0.1
	% largest unknown impurity	0.09	0.09	0.11	0.08
	% total impurities	1.2	0.5	0.7	0.4
55° C., 2 W	% Liothyronine	1.9	0.4	0.8	0.2
	% largest unknown impurity	0.1	0.1	0.11	0.1
	% total impurities	2.0	0.9	1.1	0.4

TABLE 2-continued

	Levothyroxine Na (mcg/mL)	20	20	100	20
	Tromethamine (mg/mL)	10			
	Solvent	Normal saline			
	pH	9.5	10.4	10.4	11.5
25° C., 2 M	% Liothyronine	0.34	0.17	0.23	0.34
	% largest unknown impurity	0.11	0.20	0.11	15.4
	% total impurities	0.7	0.6	0.6	19.6
40° C., 2 M	% Liothyronine	1.00	0.38	0.49	0.31
	% largest unknown impurity	0.14	0.22	0.10	9.2
	% total impurities	1.44	0.88	0.8	12.1

The results described in Table 2 demonstrate that reduced liothyronine and/or total impurities were detected in levothyroxine formulations having a pH of 10.4 as compared to pH 9.5 or 11.5 following storage at 25° C. or 40° C. for 2M.

Example 2

This example demonstrates the stability of exemplary formulations comprising levothyroxine sodium, sodium iodide, and tromethamine as a function of sodium iodide concentration and pH of the formulation.

Separate samples containing 20 mcg/mL levothyroxine sodium, 10 mg/mL tromethamine, 5.4 mg/mL sodium chloride, and sodium iodide at a concentration of 280 mcg/mL, 140 mcg/mL, or 6 mcg/mL in water were adjusted to various pH levels. 5 mL of each sample was filled into 10 cc flint molded vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at temperatures of 25° C. or 55° C. for 4 W prior to analysis by HPLC.

The HPLC conditions were as follows:

Column: ACE Excel 3 C18-PFP, 4.6×150 mm HPLC column

Mobile Phase A: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (4.0 g/800 mL/1600 mL/1600 mL/4.0 mL)

Mobile Phase B: Sodium heptanesulfonate/Acetonitrile/Water/Methanol/H_3PO_4 (4.0 g/2000 mL/200 mL/1800 mL/4.0 mL)

Diluent: 0.01 N NaOH

Column temperature: 25° C.

Flow rate: 1.5 mL/min

Injection volume: 80 µL

Autosampler temperature: 5° C.

Detection: UV at 225 nm

Separation mode: Gradient

Gradient program:

Time	% Mobile Phase	
(minutes)	A	B
0	100	0
25	100	0
40	10	90
50	10	90
51	100	0
60	100	0

The relative response time (RRT) for liothyronine to levothyroxine was approximately 0.71.

The results for liothyronine, largest any other individual impurity (AOII), and total impurities as determined by peak area percent are set forth in Table 3.

TABLE 3

	Levothyroxine Na (mcg/mL)	20						
	Tromethamine (mg/mL)	10						
	Solvent	5.4 mg/mL sodium chloride in water						
	NaI (mcg/mL)	280			140			6
	pH	9.5	10	10.5	9.5	10	10.5	10.5
25° C.,	% Liothyronine	0.28	0.26	0.26	0.28	0.27	0.26	0.25
4 W	% AOII	0.56	0.55	0.57	0.52	0.55	0.6	0.33
	% total impurities	1.58	1.61	1.66	1.51	1.64	1.75	1.9
55° C.,	% Liothyronine	1.63	1.06	0.71	1.74	1.06	0.74	0.87
4 W	% AOII	0.53	0.54	0.53	0.59	0.61	0.53	0.99
	% total impurities	3.24	2.76	2.43	3.6	2.86	2.49	3.5

The samples also were stored at temperatures of 25° C. or 40° C. for 2M or 4M prior to analysis by HPLC.

The HPLC conditions were as follows:

Column: Phenomenex Kinetex 2.6 µm C18, 4.6×150 mm HPLC column

Mobile Phase A: 0.05 M Sulfamic Acid, pH 2.0

Mobile Phase B: Acetonitrile

Diluent: 10% Mobile Phase A in Methanol: Acetonitrile: Mobile Phase A (1000 mL: 300 mL: 700 mL)

Column temperature: 27° C.

Flow rate: 1.2 mL/min

Injection volume: 50 µL

Autosampler temperature: 25° C.

Detection: UV at 225 nm

Separation mode: Gradient

Gradient program:

Time	% Mobile Phase	
(minutes)	A	B
0	70	30
5	70	30
33	32	68
35	32	68
36	70	30
50	70	30

The relative response time (RRT) for liothyronine to levothyroxine was approximately 0.62.

The results for liothyronine, largest any other individual impurity (AOII), and total impurities as determined by peak area percent are set forth in Table 4.

TABLE 4

	Levothyroxine Na (mcg/mL)	20						
	Tromethamine (mg/mL)	10						
	Solvent	5.4 mg/mL sodium chloride in water						
	NaI (mcg/mL)	280			140			6
	pH	9.5	10	10.5	9.5	10	10.5	10.5
25° C., 2 M	% Liothyronine	0.28	0.24	0.23	0.29	0.25	0.24	0.26
	% AOII	0.11	0.12	0.11	0.09	0.10	0.12	0.46
	% total impurities	0.81	0.8	0.85	0.76	0.77	0.88	1.85
40° C., 2 M	% Liothyronine	0.9	0.55	0.39	0.88	0.55	0.41	0.43
	% AOII	0.13	0.13	0.17	0.14	0.14	0.15	0.91
	% total impurities	1.56	1.2	1.07	1.42	1.18	1.09	2.5
25° C., 4 M	% Liothyronine	0.35	0.28	0.25	0.35	0.28	0.26	0.25
	% AOII	2.14	0.17	0.11	0.18	0.17	0.17	1.21
	% total impurities	3.26	0.93	1.04	1.00	0.93	0.94	2.81
40° C., 4 M	% Liothyronine	1.23	0.84	0.58	1.3	0.86	0.59	0.6
	% AOII	0.52	1.38	1.07	0.72	0.92	0.69	1.45
	% total impurities	2.76	3.23	2.72	2.84	2.73	2.14	3.51

The results described in Tables 3 and 4 demonstrate that levels of liothyronine in formulations comprising 140 mcg/mL or 280 mcg/mL sodium iodide were decreased as the pH was increased from 9.5 to 10 and from 10 to 10.5 following storage at 55° C. for 4 W or at 40° C. for 2M or 4M. The levels of total impurities in formulations comprising 140 mcg/mL sodium iodide also were decreased as the pH was increased from 9.5 to 10 and from 10 to 10.5 following storage at 55° C. for 4 W or at 40° C. for 2M or 4M. Lower levels of AOII and total impurities were detected in formulations comprising 140 mcg/mL or 280 mcg/mL sodium iodide at pH 10.5 as compared to formulations comprising 6 mcg/mL sodium iodide at pH 10.5 following storage at 55° C.° for 4 W or at 40° C. for 2M or 4M.

Example 4

This example demonstrates the stability of exemplary formulations comprising levothyroxine sodium, sodium iodide, and tromethamine as a function of vial type.

An aqueous solution containing 20 mcg/mL levothyroxine sodium, 10 mg/mL tromethamine, 5.4 mg/mL sodium chloride, and 6 mcg/mL sodium iodide was adjusted to pH 10.5. 5 mL of the solution was filled into each of the vials described in Table 5, and the vials were stoppered under nitrogen.

TABLE 5

	Type	Size	Color	Glass vial preparation	Inner surface treatment
Vial 1	Glass	10 cc	Flint	Molded	No
Vial 2	Glass	10 cc	Amber	Molded	$(NH_4)_2SO_4$
Vial 3	Glass	5 cc	Amber	Tubing	$(NH_4)_2SO_4$
Vial 4	Glass	6 cc	Flint	Molded	No
Vial 5	Plastic[1]	10 cc	Opaque	N/A	N/A
Vial 6	Plastic[2]	10 cc	Opaque	N/A	N/A
Vial 7	Plastic[3]	10 cc	Clear	N/A	N/A
Vial 8	Plastic[3]	10 cc	Amber	N/A	N/A
Vial 9	Plastic[4]	10 cc	Clear	N/A	Silicon
Vial 10	Plastic[4]	10 cc	Amber	N/A	Silicon

[1]polypropylene copolymer - ExxonMobil PP9122
[2]polypropylene copolymer - Flint Hills Resources 23M2A
[3]cyclic olefin polymer - Daikyo CRYSTAL ZENITH™
[4]cyclic olefin polymer - SiO_2 Medical Products

The vials were stored at a temperature of 25° C. or 55° C. for 4 W prior to analysis by HPLC. The HPLC conditions were the same as described hereinabove for the data of Table 3. The results for liothyronine (T3), largest any other individual impurity (AOII), and total impurities as determined by peak area percent are set forth in Table 6.

TABLE 6

	Storage Temp					
	25° C.			55° C.		
Impurity	T3	AOII	Tot	T3	AOII	Tot
Vial 1	0.25	0.33	1.9	0.87	0.99	3.5
Vial 2	0.28	0.39	2	1.59	4.97	14.6
Vial 3	0.25	2.54	4.4	0.91	2.31	4.9
Vial 4	0.22	0.52	2.5	1.11	4.02	7.9
Vial 5	0.25	0.7	3.4	0.85	8.76	20.3
Vial 6	0.25	0.89	3.7	0.73	10.51	29.9
Vial 7	0.24	0.75	2.6	0.78	7.29	10.7
Vial 8	0.24	0.81	2.7	0.75	7.09	10.6
Vial 9	0.25	0.48	1.9	0.78	2.79	5.4
Vial 10	NT	NT	NT	0.76	3	5.7

The results described in Table 6 demonstrate that vial material, size, color, and/or treatment can affect the stability of formulations comprising levothyroxine sodium, sodium iodide, and tromethamine.

Example 5

This example demonstrates the stability of comparative formulations comprising levothyroxine sodium, glycerol, sodium chloride, and water as a function of the pH of the formulation.

Separate samples containing levothyroxine sodium at a concentration of 20 mcg/mL and glycerol at a concentration of 100 mg/mL in normal saline were adjusted to pH levels of 7, 8, and 9. 5 mL of each sample was filled into 10 cc amber tubing vials, and the vials were stoppered with 20 mm stoppers under nitrogen. The samples were stored at a temperature of 55° C. The samples were analyzed by HPLC at 1 week of storage using the HPLC conditions described in Example 1. The results for liothyronine, largest unknown impurity, and total impurities as determined by peak area percent are set forth in Table 7.

TABLE 7

	Levothyroxine Na (mcg/mL)	20		
	Glycerol (mg/mL)	100		
	Solvent	Normal saline		
	pH	7	8	9
55° C., 1 W	% Liothyronine	3.6	3.4	2.4
	% largest unknown impurity	1.16	1.30	0.82
	% total impurities	5.3	5.4	3.8

The results described in Table 7 demonstrate that high levels of impurities are formed in levothyroxine formulations containing glycerol over the pH range 7-9 following storage at 55° C. for one week.

Example 6

This example demonstrates a method for preparing an exemplary formulation of the invention.

The composition of an exemplary formulation containing 100 mcg levothyroxine in 5 mL volume is as described in Table 8.

TABLE 8

Component	Quantity per mL
Levothyroxine sodium, USP	20 mcg
Sodium chloride	6.48 mg
Sodium iodide	0.14 mg
Tromethamine, USP	10 mg
Sodium hydroxide (1N)	As needed to adjust pH to 10-10.5
Hydrochloric acid (1N)	(target 10.3)
Purified water	q.s.

The compositions for exemplary formulations containing 200 mcg or 500 mcg levothyroxine in 5 mL volume are the same as described in Table 8, except that the concentrations of levothyroxine sodium are 40 mcg/mL and 100 mcg/mL, respectively.

An exemplary formulation is prepared by filling purified water in an amount of approximately 80% of a predetermined final batch volume into a suitable container. The entire amounts of sodium chloride, sodium iodide, and tromethamine are added in succession, with mixing until dissolution of each ingredient prior to addition of the next ingredient. The pH is determined, and then adjusted to pH 10.3 (range of 10.0 to 10.5) with sodium hydroxide and/or hydrochloric acid. The entire amount of levothyroxine sodium is added to the container, and the solution is mixed until dissolution. The pH is determined, and then adjusted to pH 10.3 (range of 10.0 to 10.5) with sodium hydroxide and/or hydrochloric acid. Purified water is added in an amount sufficient to reach the predetermined batch volume with continued mixing to ensure complete dissolution of all ingredients. The formulation can be bubbled with nitrogen or other suitable gas throughout the compounding to limit the dissolved oxygen in the formulation. Under aseptic conditions, the solution is filtered through a 0.22 μm filter, and then 5 mL of the filtered solution is filled into containers (e.g. vials) under nitrogen. The containers are then sealed (e.g., stoppered) under nitrogen.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term "at least one" followed by a list of one or more items (for example, "at least one of A and B") is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

The invention claimed is:

1. A pharmaceutical product comprising a liquid formulation comprising levothyroxine or a pharmaceutically acceptable salt thereof, a stabilizing agent comprising an amine selected from one or more of tromethamine, bis(2-hydroxyethyl)-imino-tris(hydroxymethyl)methane, monoethanolamine, diethanolamine, triethanolamine, 2-amino-2-methyl-1,3-propanediol, 2-dimethylamino-2-methyl-1-propanediol, 2-amino-2-ethylpropanol, 2-amino-1-butanol, and 2-amino-2-methyl-1-propanol, and water, wherein the formulation retains at least 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for two months at 40° C. and retains at least 95% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for at least 12 months at room temperature.

2. The pharmaceutical product of claim **1**, wherein the levothyroxine or a pharmaceutically acceptable salt thereof is levothyroxine sodium.

3. The pharmaceutical product of claim **2**, wherein levothyroxine sodium is present at a concentration of from about 5 mcg/mL to about 500 mcg/mL.

4. The pharmaceutical product of claim **1**, wherein the amine is tromethamine which is present at a concentration of about 1 mg/mL to about 50 mg/mL.

5. The pharmaceutical product of claim **1**, wherein the stabilizing agent further comprises a salt of iodine.

6. The pharmaceutical product of claim **5**, wherein the salt of iodine is sodium iodide or potassium iodide.

7. The pharmaceutical product of claim **6**, wherein the salt of iodine is sodium iodide which is present at a concentration of about 10 mcg/mL to about 500 mcg/mL.

8. The pharmaceutical product of claim **1**, wherein the formulation has a pH of from about 9.0 to about 11.5.

9. The pharmaceutical product of claim **8**, wherein the formulation has a pH of from about 9.8 to about 10.8.

10. The pharmaceutical product of claim **1**, wherein the formulation contains not more than 2.0% liothyronine (T3).

11. The pharmaceutical product of claim **1**, wherein the formulation contains not more than 5.0% total impurities.

12. The pharmaceutical product of claim **1**, wherein the formulation retains at least about 90% of the initial concentration of levothyroxine or pharmaceutically acceptable salt thereof after storage for at least 18 months at room temperature.

13. The pharmaceutical product of claim **1**, wherein the formulation does not contain a buffer.

14. The pharmaceutical product of claim **1**, wherein the formulation is contained within a clear glass container.

15. The pharmaceutical product of claim **14**, wherein the clear glass container is a flint colored, molded vial, ampoule, cartridge, or syringe.

16. The pharmaceutical product of claim **14**, wherein the clear glass container is not treated with ammonium sulfate.

* * * * *

JS 44 (Rev. 04/21)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

FRESENIUS KABI USA, LLC

(b) County of Residence of First Listed Plaintiff Lake County, Illinois
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Ahmed M.T. Riaz, ArentFox Schiff LLP, 1301 6th Ave., 42nd Floor, New York, NY 10019 (212) 484-3900

DEFENDANTS

ACCORD HEALTHCARE INC.

County of Residence of First Listed Defendant Wake County, North Carolina
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*
Richard Ruzich, Taft Stettenius & Hollister LLP, 111 E. Wacker Dr. Suite 2600, Chicago, IL 60601-4208 (312) 836-4012

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

INTELLECTUAL PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☒ 835 Patent - Abbreviated New Drug Application
- ☐ 840 Trademark
- ☐ 880 Defend Trade Secrets Act of 2016

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 376 Qui Tam (31 USC 3729(a))
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit (15 USC 1681 or 1692)
- ☐ 485 Telephone Consumer Protection Act
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation - Transfer ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. Section 271

Brief description of cause:
Patent Infringement

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:

JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE Hon. Susan D. Wigenton, U.S.D.J. DOCKET NUMBER 2:20-cv-15342

DATE 04/26/2024

SIGNATURE OF ATTORNEY OF RECORD
s/ Ahmed M.T. Riaz

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; **NOTE: federal question actions take precedence over diversity cases.**)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If there are multiple nature of suit codes associated with the case, pick the nature of suit code that is most applicable. Click here for: Nature of Suit Code Descriptions.

V. Origin. Place an "X" in one of the seven boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation – Transfer. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407.
Multidistrict Litigation – Direct File. (8) Check this box when a multidistrict case is filed in the same district as the Master MDL docket. **PLEASE NOTE THAT THERE IS NOT AN ORIGIN CODE 7.** Origin Code 7 was used for historical records and is no longer relevant due to changes in statute.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service.

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related cases, if any. If there are related cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.