



US009168238B2

(12) **United States Patent**
Jiang et al.(10) **Patent No.:** **US 9,168,238 B2**
(45) **Date of Patent:** ***Oct. 27, 2015**(54) **LEVOTHYROXINE FORMULATIONS**

OTHER PUBLICATIONS

- (71) Applicant: **FRESENIUS KABI USA, LLC**, Lake Zurich, IL (US)
- (72) Inventors: **John Zhiqiang Jiang**, Skokie, IL (US); **Arunya Usayapant**, Mundelein, IL (US); **George Monen**, Woodridge, 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.

U.S. Appl. No. 14/658,058, filed Mar. 2015, Jiang et al.*

APP Pharmaceuticals, LLC, "Highlights of Prescribing Information," 2011, pp. 1-11.

APP Pharmaceuticals, LLC, "Levothyroxine Sodium for Injection", 2008, pp. 1-3.

Baheti, et al., "Excipients used in lyophilization of small molecules," "J. Excipients and Food Chem.," 2010, pp. 41-54, vol. 1, No. 1.

Bedford Laboratories, "Levothyroxine Sodium for Injection," 2003, pp. 1-2.

Schering Corporation, "Leventa—levothyroxine sodium solution," 2010, pp. 1-3.

Vidya Medical News Service, "Synthroid, The Most Commonly Prescribed Medication in the US," 2000, pp. 1-11.

International Searching Authority, "International Search Report and Written Opinion for PCT/US2012/052838," Nov. 16, 2012, Publisher: European Patent Office, Published in: EP.

Collier, et al., "Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate," "APPS PharmSiTech," May 8, 2010, pp. 818-825, vol. 11, No. 2.

Rowe, et al., "Mannitol," "Handbook of Pharmaceutical Excipients," 2006, pp. 449-453.

Beth D. Herman et al., The Effect of Bulking Agent on the Solid-State Stability of Freeze-Dried Methylprednisolone Sodium Succinate, Pharmaceutical Research, vol. 11, No. 10, pp. 1467-1473 (May 11, 1994).

Alexandra I. Kim et al., The physical state of mannitol after freeze-drying: effects of mannitol concentration, freezing rate, and a noncrystallizing cosolute, Journal of Pharmaceutical Sciences, vol. 87, No. 8, pp. 931-935 (May 11, 1998).

Searles, JA., "Freezing and Annealing Phenomena in Lyophilization," Freeze Drying/Lyophilization of Pharmaceutical and Biological Products, 3rd Edition. Ed. Louis Rey, Ed. Joan C. May. London: Informa Healthcare, 2010, 52-81.

Won, CM., "Kinetics of Degradation of Levothyroxine in Aqueous Solution and in Solid State," Pharm. Res., 9: 131-137 (1992).

SYNTHROID® Injection (levothyroxine sodium), Physicians' Desk Reference, Medical Economics, 1970 (3 pages).

LEVOTHROID® (levothyroxine sodium) For Injection, Physicians' Desk Reference, Medical Economics, 1986 (3 pages).

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Synthroid® (Levothyroxine Sodium tablets, USP) Application No. 21-402, 2002 (17 pages).

Gieseler et al., "Influence of Common Excipients on the Crystalline Modification of Freeze-Dried Mannitol," Pharmaceutical Technology, 3(32) (Mar. 2, 2008) (4 pages).

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(5-6): 697-711 (Jul. 2001) (15 pages).

Patel et al., "The Effect of Excipients on the Stability of Levothyroxine Sodium Pentahydrate Tablets," Int. J. Pharm., 264(1-2), pp. 35-43 (Oct. 2, 2003) (9 pages).

(Continued)

(21) Appl. No.: **14/641,426**(22) Filed: **Mar. 8, 2015**

(65) **Prior Publication Data**
US 2015/0174246 A1 Jun. 25, 2015

Related U.S. Application Data

- (63) Continuation of application No. 13/597,884, filed on Aug. 29, 2012, now Pat. No. 9,006,289.
- (60) Provisional application No. 61/529,084, filed on Aug. 30, 2011.

- (51) **Int. Cl.**
A61K 31/198 (2006.01)
A61K 47/26 (2006.01)
A61K 9/00 (2006.01)
A61K 9/19 (2006.01)
A61K 47/02 (2006.01)
A61K 47/10 (2006.01)

- (52) **U.S. Cl.**
CPC **A61K 31/198** (2013.01); **A61K 9/0019** (2013.01); **A61K 9/19** (2013.01); **A61K 47/02** (2013.01); **A61K 47/10** (2013.01); **A61K 47/26** (2013.01)

- (58) **Field of Classification Search**
CPC ... **A61K 31/198**; **A61K 47/26**; **A61K 9/0019**; **A61K 9/19**
IPC **A61K 31/198**, **47/26**, **9/0019**, **9/19**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,225,204 A 7/1993 Chen et al.
5,955,105 A 9/1999 Mitra et al.
6,936,274 B2 8/2005 Hanshew, Jr. et al.
8,318,712 B2 11/2012 Pierres et al.
9,006,289 B2 * 4/2015 Jiang et al. 514/567
2012/0190748 A1 7/2012 Treasurer

FOREIGN PATENT DOCUMENTS

JP 2002284679 10/2002

Primary Examiner — Kara R McMillian

(74) Attorney, Agent, or Firm — Baker & Hostetler LLP

(57) **ABSTRACT**

A levothyroxine composition includes levothyroxine sodium and mannitol. The composition is a lyophilized solid. The composition may include from 100 to 500 micrograms levothyroxine sodium and from 2 to 4 milligrams mannitol.

30 Claims, 3 Drawing Sheets

(56)

References Cited**OTHER PUBLICATIONS**

Stadlman et al., "Stability of Levothyroxine Sodium 0.4 microg/mL in 0.9% Sodium Chloride Injection," *Prog. Transplant.*, 19(4), pp. 354-357 (Dec. 2009) (4 pages).

Strong et al., "Stability of Levothyroxine in Sodium Chloride for IV Administration," *Can. J. Hosp. Pharm.*, 63(6), p. 437-443 (Nov. 2010) (7 pages).

United States Pharmacopeia and National Formulary (Revision Bulletin) Rockville, MD: United States Pharmacopeia Convention; Levothyroxine pp. 1-3 (Oct. 1, 2010) (3 pages).

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "Chemistry Review(s)," Levothyroxine Sodium for Injection, Application No. 202231, Jun. 2011 (41 pages).

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "Summary Review," Levothyroxine Sodium for Injection, Application No. 202231, Jun. 2011 (12 pages).

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products," Revision 2, Nov. 2003 (25 pages).

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "Guidance for Industry: Q8(R2) Pharmaceutical Development," Revision 2, Nov. 2009 (29 pages).

Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products 2nd Edition, vol. 6 (Niazi ed.), pp. 315-317 (Sep. 2009), ISBN: 9781420081305 (5 pages).

Intravenous Therapy: A Comprehensive Application of Intravenous Therapy and Medication Administration (Nentwich ed.), pp. 357-358 (Mar. 1990), ISBN: 0867204192 (4 pages).

Delmar Nurse's Drug Handbook, 2009 Edition (Spratto et al. ed.), pp. 967-969, ISBN-13: 9781428361065 (5 pages).

LEVO-T® (levothyroxine sodium tablets, USP) Prescribing Information, 2002 (17 pages).

LEVOXYL® (levothyroxine sodium tablets, USP) Prescribing Information, 2001 (12 pages).

SYNTHROID® (levothyroxine sodium tablets, USP) Prescribing Information, 2002 (19 pages).

THYRO-TABS® (levothyroxine sodium tablets, USP) Prescribing Information, 2002 (14 pages).

UNITHROID® (levothyroxine sodium tablets, USP) Prescribing Information, 2000 (14 pages).

* cited by examiner

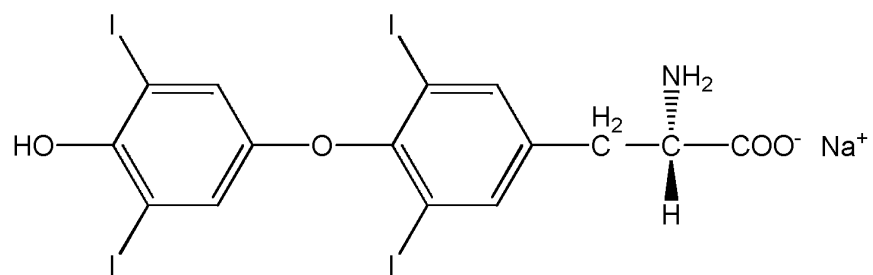


FIG. 1

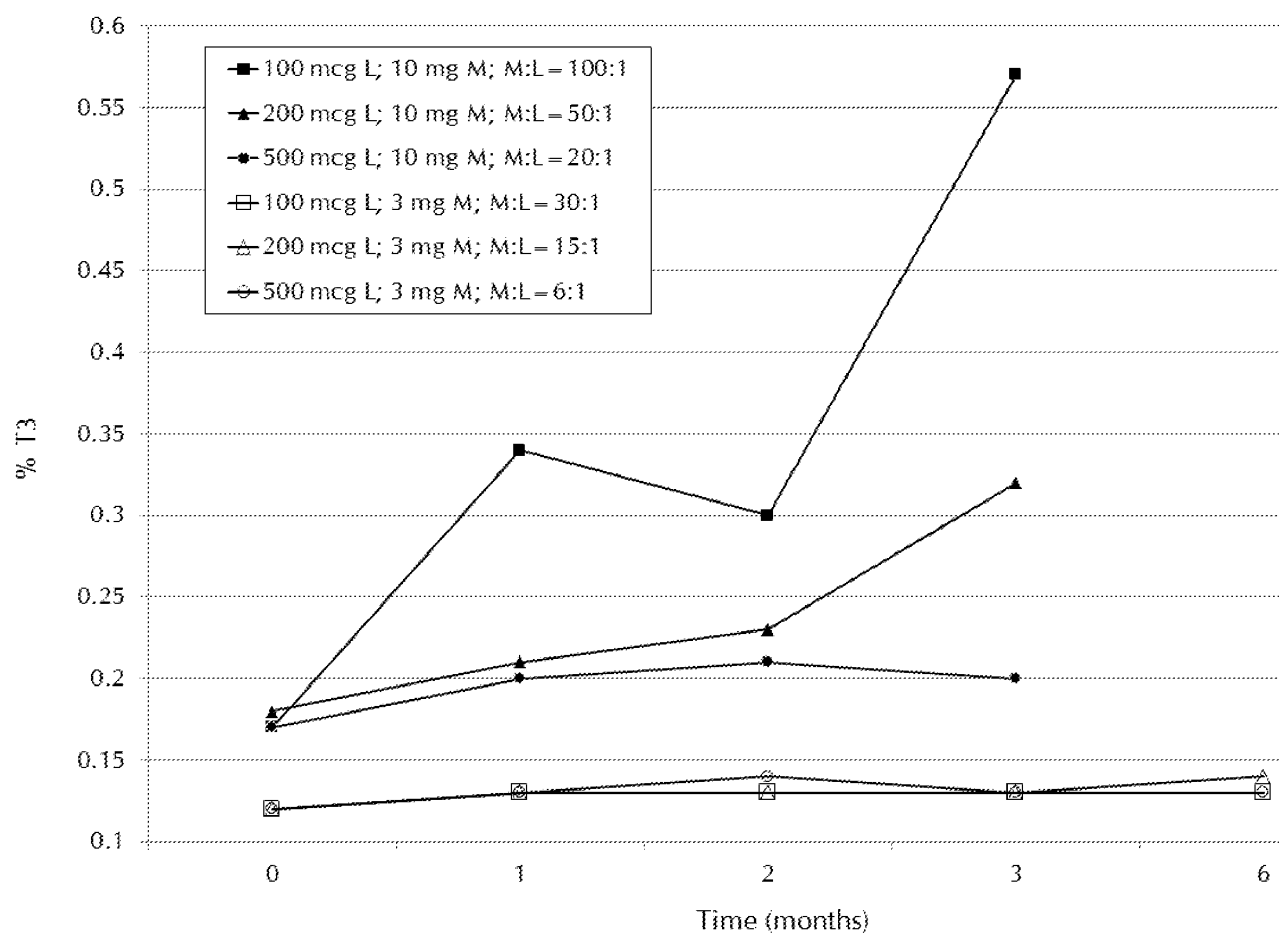


FIG. 2

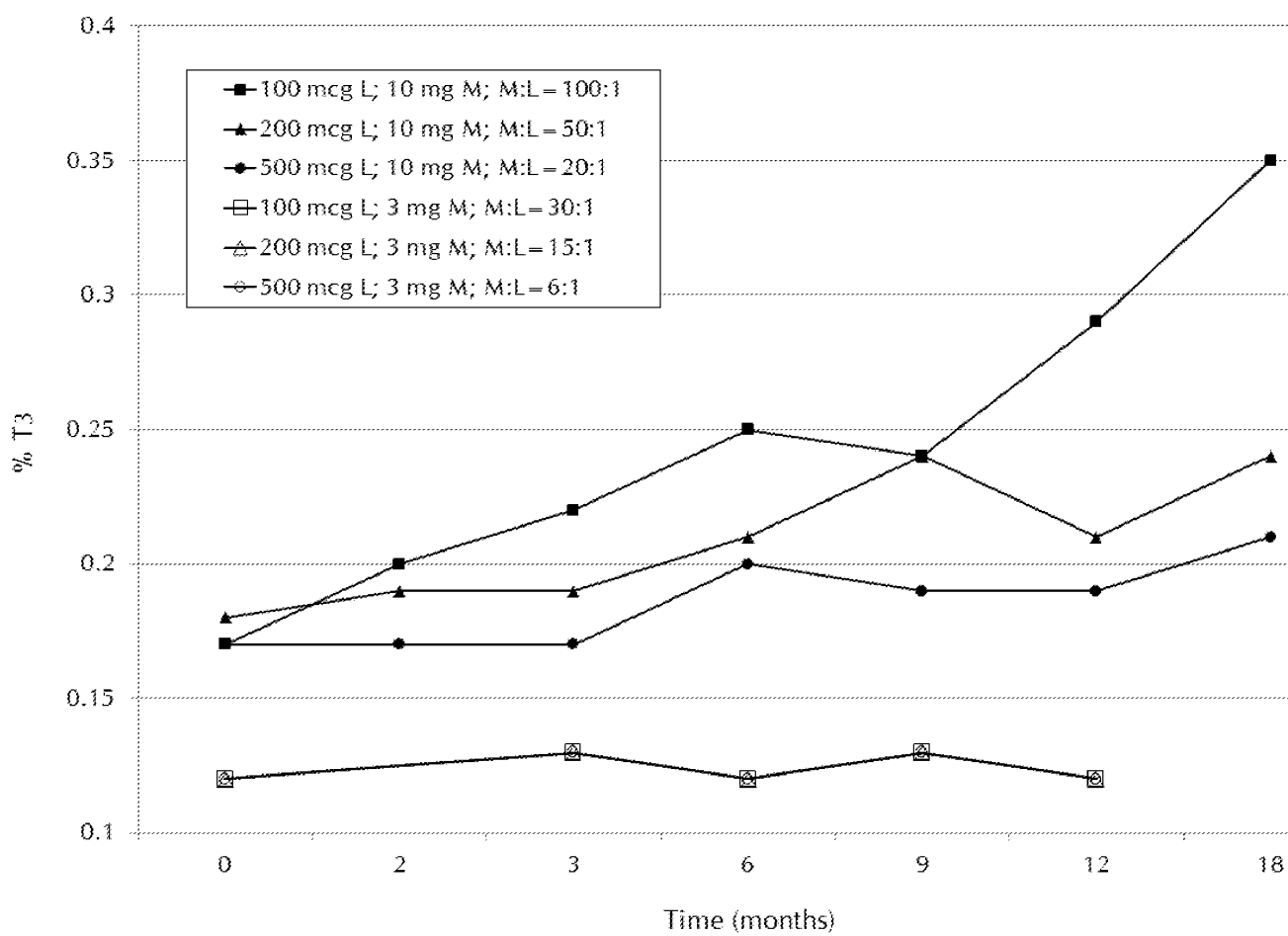


FIG. 3



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.