(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 January 2017 (26.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/013591 A1

(51) International Patent Classification:
*A61K 31/00* (2006.01)

(21) International Application Number:
PCT/IB2016/054308

(22) International Filing Date:
20 July 2016 (20.07.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3770/CHE/2015 22 July 2015 (22.07.2015) IN

(71) Applicant: **LEIUTIS PHARMACEUTICALS PVT LTD** [IN/IN]; Plot No 23, VSR Complex, TIE 1st Phase, Balanagar, Hyderabad, Telangana 500037 (IN).

(72) Inventors: **CHANDRASHEKHAR, Kocherlakota**; Plot-13, Sonali Cooperative Housing Society, Bhavana Enclave, Bowenpally, Tarbund, Secunderabad, Telangana 500009 (IN). **NAGARAJU, Banda**; Flat 301, Kamalakar Rao Classic, Sapthagiri Colony, Kukatpally, Hyderabad, Telangana 500072 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *of inventorship (Rule 4.17(iv))*

**Published**:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2017/013591 A1

(54) Title: STABILIZED LIQUID FORMULATION OF LEVOTHYROXINE

(57) Abstract: The present invention relates to stabilized liquid formulations of Levothyroxine or a pharmaceutically acceptable salt thereof, intended for parenteral administration. Further this invention also describes process of preparing such compositions.

# STABILIZED LIQUID FORMULATION OF LEVOTHYROXINE

## Background of the Invention

Thyroxine active drugs are known for both therapeutic and prophylactic treatment of thyroid disorders. The thyroid accomplishes its regulation functions by producing the hormones L-triiodothyronine (liothyronine; T3) and L-thyroxine (levothyroxine; T4). The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.

Administration of levothyroxine sodium provides T4 to a patient. Once absorbed, the administered T4 behaves identically to T4 that otherwise would be secreted by the thyroid gland of the patient, and binds to the same serum proteins, providing a supply of circulating T4-thyroglobulin in the patient. The administered T4 may be deiodinated in vivo to T3. As a result, a patient receiving appropriate doses of levothyroxine sodium will exhibit normal blood levels of T3, even when the patient's thyroid gland has been removed or is not functioning.

Levothyroxine sodium is prescribed for thyroid hormone replacement therapy in cases of reduced or absent thyroid function e.g., ailments such as myxedema, cretinism and obesity. Levothyroxine sodium is quite unstable, hygroscopic and degrades rapidly when subjected to high humidity, light or high temperature. Because of the physicochemical properties of the drug, formulations of levothyroxine sodium have extremely short stability duration, worsened under conditions of high humidity and temperature.

Levothyroxine sodium is available in the form of capsules, tablets and parenteral dosage forms. Levothyroxine sodium for injection is available as sterile lyophilized product for parenteral administration containing 100 mcg/vial, 200 mcg/vial and 500 mcg/vial.

Conventional formulations of levothyroxine sodium for injection are preservative-free lyophilized powders containing synthetic crystalline levothyroxine sodium, mannitol, tribasic sodium phosphate, and sodium hydroxide. These conventional formulations typically contain 10mg mannitol, 700µg of tribasic sodium phosphate and 100mcg or 200mcg or 500mcg of levothyroxine sodium. Administration of the conventional formulation involves reconstitution of the lyophilized powder in 5mL of 0.9% sodium chloride injection, to provide injectable solutions having levothyroxine sodium concentrations of 20mcg/mL, 40mcg/mL or 100mcg/mL.

U.S Pat. No. 9,006,289, issued on April 14, 2015, to Jiang, et al., discloses lyophilized composition comprising of levothyroxine sodium, a phosphate buffer and mannitol.

Levothyroxine has extremely short stability, worsened under conditions of high humidity and temperature. Due to this instability, Levothyroxine injectable formulations are used in the form of lyophilized formulations that are dissolved in 0.9% sodium chloride Injection immediately before injection. The present inventors have developed stable liquid formulations of Levothyroxine intended for parenteral administration.

**Summary of the Invention**

One object of the invention provides stable liquid parenteral pharmaceutical formulation of Levothyroxine.

Another aspect of the invention provides stable liquid parenteral pharmaceutical formulation of Levothyroxine comprising Levothyroxine, buffering agents, one or more solvents and other pharmaceutically acceptable excipients thereof.

Yet another aspect of the invention provides liquid parenteral pharmaceutical formulation of Levothyroxine comprising Levothyroxine sodium, buffering agents, stabilizing agents, one or more solvents and other pharmaceutically acceptable excipients thereof.

**Detailed description of the Invention**

The present invention relates to stable liquid parenteral formulation of Levothyroxine, and more particularly to stable Levothyroxine liquid formulation comprising of buffering agents, stabilizing agents, solvents and other pharmaceutically acceptable excipients thereof.

In the context of this invention "Levothyroxine" refers to the pharmaceutically acceptable salts, solvates, hydrates and anhydrous forms thereof. The formulations of the present invention preferably comprise Levothyroxine sodium.

As used herein, "liquid parenteral formulations of Levothyroxine" refers to formulations that contain Levothyroxine in dissolved or solubilised form and are intended to be used as such or upon dilution in intravenous diluents.

Levothyroxine sodium is quite unstable, hygroscopic and degrades rapidly when subjected to high humidity, light or high temperature. Degradation is further enhanced by the presence of water. Hence, attempts to develop an intravenous preparation of Levothyroxine were limited.

The inventors of the present invention have surprisingly found that it is possible to develop stable liquid parenteral pharmaceutical formulation of Levothyroxine, despite its rapid degrading nature.

One embodiment of the invention relates to liquid parenteral pharmaceutical formulations of Levothyroxine comprising:

i. Levothyroxine
ii. buffering agents
iii. one or more solvents and

other pharmaceutically acceptable excipients thereof.

Yet another embodiment of the invention relates to liquid parenteral pharmaceutical formulation of Levothyroxine comprising:

i. Levothyroxine sodium
ii. buffering agents,
iii. stabilizing agents and/or solubilizing agents
iv. one or more solvents and
v. optionally one or more pharmaceutically acceptable excipients selected from pH adjusting agents and anti-oxidants.

Stabilizing agents used in the formulation include, but not limited to sodium iodide, potassium iodide and the like. The pharmaceutical compositions of the present invention may also contain solubilizing agents such as cyclodextrins. These agents may be used in the formulation to maintain the solubility and stability of levothyroxine sodium during the entire shelf life of the formulation. Suitable cyclodextrins include but not limited to α, β and γ-cyclodextrin and cyclodextrins modified with alkyl-, hydroxyalkyl-, dialkyl-, and sulfoalkyl-ether modified cyclodextrins such as methyl or hydroxypropyl β-cyclodextrins (HPβCD), methyl-and-ethyl-β-cyclodextrin, sulfoalkylether-substituted beta-cyclodextrin, sulfobutylether-β-cyclodextrin (SBECD) and the like.

Suitable buffering agents include amino acids such as arginine, alanine, histidine, glycine and lysine; citrate, glutamate, bicarbonate, tartrate, benzoate, lactate, gluconate, TRIS, acetate, meglumine, borate and phosphate buffer.

Suitable solvents include, but not limited to dimethylacetamide, dimethyl sulfoxide, N-methylpyrrolidone, dimethylisosorbide, ethanol, propylene glycol, polyethylene alcohol, propylene glycol esters, polyethylene glycols, glycerine, water and the like. Preferred solvents are water and propylene glycol.

Suitable pH adjusting agents include sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, ammonium carbonate, hydrochloric acid, citric acid, lactic acid, phosphoric acid, sodium phosphate, sulfuric acid and the like.

The pharmaceutical compositions of the present invention may also contain one or more anti-oxidants such as sodium sulfite, sodium bisulfite, sodium metabisulfite, sodium thiosulphate, sodium formaldehyde sulfoxylate, citric acid, tocopherol, butylated hydroxy anisole, butylated hydroxy toluene, monothioglycerol, ascorbic acid, sodium ascorbate and propyl gallate.

The inventors carried out experiments with various buffering agents to determine suitable buffering agent in the final formulation. Levothyroxine formulations prepared were tested for stability at 60±2°C (3 days). The data is summarized in table 1.

Table 1: Evaluation of different buffering agents for their suitability in the formulation.

| **Ingredients** | **Quantity in mg** | | | | | |
|---|---|---|---|---|---|---|
| | **A1** | **A2** | **A3** | **A4** | **A5** | **A6** |
| Levothyroxine sodium | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.5 |
| Arginine | 10 | - | - | - | - | - |
| Sodium carbonate buffer | - | 10 | - | - | - | - |
| Sodium hydrogen carbonate buffer | - | - | 10 | - | - | - |
| Tris buffer | - | - | - | 8 | - | - |
| Tri basic sodium phosphate dodeca hydrate buffer | - | - | - | - | 2.3 | - |
| Meglumine buffer | - | - | - | - | - | 1 |
| Mannitol | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | - |
| Sodium hydroxide | q.s to adjust the pH 11.0±1.0 | | | | | |
| Water for Injection | Qs to 1ml | | | | | |
| **Observations** | | | | | | |
| **60±2°C (3 days)** | | | | | | |
| Total impurities | 3.14 | 5.49 | 6.42 | 5.82 | 11.99 | 4.8 |

A preferred embodiment of the invention relates to liquid parenteral pharmaceutical formulation of Levothyroxine comprising:

i. Levothyroxine sodium

ii. stabilizing agents and/or solubilizing agents selected from sodium iodide, potassium iodide and cyclodextrins
iii. buffering agent(s) selected from aminoacids such as arginine, alanine, histidine, glycine and lysine; citrate, glutamate, bicarbonate, tartrate, benzoate, lactate, gluconate, TRIS, acetate, borate and phosphate buffer
iv. one or more solvents selected from the group comprising water, polyethylene glycol, ethanol, propylene glycol and glycerine
v. optionally one or more pharmaceutically acceptable excipients selected from pH adjusting agents and anti-oxidants.

Levothyroxine formulation prepared according to the invention was tested for stability at 2-8°C, 25°C and 60°C for a period of 1 month. The stability data of the invention formulation is summarized in table 2.

Table 2: Stability data of the product prepared according to example 5

| **Levothyroxine sodium Invention formulation stability data** | | | | | | |
|---|---|---|---|---|---|---|
| Storage condition | 2-8°C | 2-8°C | 25°C | 25°C | 60°C | 60°C |
| Storage duration | 1 week | 1 month | 1 week | 1 month | 1 week | 1 month |
| Total impurities | 0.39 | 0.50 | 0.43 | 0.55 | 0.58 | 1.10 |
| pH | 6.25 | 6.40 | 6.67 | 6.81 | 6.21 | 6.47 |
| Osmolality (mOsm/kg) | 272 | 255 | 263 | 238 | 266 | 262 |

Surprisingly no significant increase in impurities was observed even at accelerated conditions. The data confirms the inventors' finding that Levothyroxine formulations in the presence of suitable excipients resulted in a stable product.

The following examples further describe certain specific aspects and embodiments of the present invention and demonstrate the practice and advantages thereof. It is to be understood that the examples are given by way of illustration only and are not intended to limit the scope of the invention in any manner.

**Example 1**

| Ingredients | Quantity |
|---|---|
| Levothyroxine sodium | 0.01-1 mg |
| Arginine | 0.01 - 4 mg |
| Propylene glycol | 0.01 - 1 ml |
| Sodium hydroxide | qs |
| Water for injection | Qs to 0.1 - 2ml |

**Manufacturing process**

Water for injection was taken in a compounding vessel and arginine was added and stirred. Propylene glycol was added to the above solution and stirred. Then the bulk solution was cooled to 2°C to 8°C. Levothyroxine sodium was added and stirred till a clear solution was obtained, while maintaining the temperature at 5±3ºC. pH of the solution was adjusted to 11 ± 1.0 by the addition of sodium hydroxide solution. The solution was filtered, followed by stoppering and sealing of the vials.

**Example 2**

| Ingredients | Quantity |
|---|---|
| Levothyroxine sodium | 0.01-1 mg |
| Alanine | 0.006 - 4 mg |
| Propylene glycol | 0.01 - 1 ml |
| Sodium hydroxide | qs |
| Water for injection | Qs to 0.1 - 2ml |

**Manufacturing process**

Water for injection was taken in a compounding vessel and alanine was added and stirred. Propylene glycol was added to the above solution and stirred. Then the bulk solution was cooled to 2°C to 8°C. Levothyroxine sodium was added and stirred till a clear solution was obtained, while maintaining the temperature at 5±3ºC. The solution was filtered, followed by stoppering and sealing of the vials.

**Example 3**

| Ingredients | Quantity |
|---|---|
| Levothyroxine sodium | 0.01-1 mg |
| L-Arginine | 250mcg |
| Sodium acetate anhydrous | 10500 mcg |
| Potassium hydroxide | 1500mcg |
| Sodium metabisulfite | 500 mcg |
| Sodium iodide | 1000mcg |
| Water for injection | Qs to 0.1 - 6ml |

**Manufacturing process**

L-Arginine was added to the manufacturing vessel containing water for injection, sodium acetate anhydrous was added to the above solution and stirred well. Potassium hydroxide was added to the above solution followed by the addition of sodium metabisulfite and sodium iodide. The solution was cooled to 2-8°C. Levothyroxine sodium was added to the above solution and stirred till a homogeneous solution was obtained.

**Example 4**

| Ingredients | Quantity |
|---|---|
| Levothyroxine sodium | 0.01-1 mg |
| Arginine | 250mcg |
| Sodium acetate anhydrous | 10500 mcg |
| Potassium hydroxide | 1500mcg |
| Sodium iodide | 1000mcg |
| Water for injection | Qs to 0.1 - 6ml |

**Manufacturing process**

Arginine was added to the manufacturing vessel containing water for injection, sodium acetate anhydrous was added to the above solution and stirred well. Potassium hydroxide was added to the above solution followed by the addition of sodium iodide.

The solution was cooled to 2-8°C. Levothyroxine sodium was added to the above solution and stirred till a homogeneous solution was obtained.

**Example 5**

| **Ingredients** | **Quantity** |
|---|---|
| Levothyroxine sodium | 0.01-1 mg |
| Arginine | 0.05mg |
| Sulfobutylether-β-cyclodextrin (SBECD) | 83.9mg |
| Sodium iodide | 2.00mg |
| Water for injection | Qs to 0.1 - 3ml |

**Brief Manufacturing Process**

SBECD was added to the manufacturing vessel containing water for injection followed by the addition of Levothyroxine sodium. Arginine was added and stirred well, till a clear solution was obtained. Sodium iodide was added to the above solution. The pH of the solution was adjusted to 6.0 ± 1.0 (if necessary) with sodium hydroxide/hydrochloric acid.

We claim

Claim 1: A stable liquid parenteral pharmaceutical formulation of Levothyroxine comprising Levothyroxine and other pharmaceutically acceptable excipients thereof.

Claim 2: A stable, liquid parenteral pharmaceutical formulation of Levothyroxine comprising

(i) Levothyroxine
(ii) Buffering agents
(iii) one or more solvents and
(iv) one or more pharmaceutically acceptable excipients thereof.

Claim 3: A stable, liquid parenteral pharmaceutical formulation of Levothyoxine comprising

(i) Levothyroxine sodium
(ii) stabilizing agents and/or solubilizing agents
(iii) buffering agents
(iv) one or more solvents
(v) optionally one or more pharmaceutically acceptable excipients selected from pH adjusting agents and anti-oxidants.

Claim 4: A stable, liquid parenteral pharmaceutical formulation of claim 3, comprising

(i) Levothyroxine sodium
(ii) stabilizing agents and/or solubilizing agents selected from sodium iodide, potassium iodide and cyclodextrins
(iii) buffering agent(s) selected from aminoacids such as arginine, alanine, histidine, glycine and lysine; citrate, glutamate, bicarbonate, tartrate, benzoate, lactate, gluconate, TRIS, acetate, meglumine, borate and phosphate buffer.
(iv) one or more solvents selected from the group comprising water, polyethylene glycol, ethanol, propylene glycol and glycerine

(v) optionally one or more pharmaceutically acceptable excipients selected from pH adjusting agents and anti-oxidants.

Claim 5: A stable, liquid parenteral pharmaceutical formulation of Levothyroxine comprising

(i) Levothyroxine sodium
(ii) sodium iodide
(iii) cyclodextrin
(iv) arginine
(v) one or more solvents selected from water, propylene glycol ethanol, polyethylene glycol and glycerine.

Claim 6: A stable, liquid parenteral pharmaceutical formulation of claims 4 and 5, wherein the cyclodextrin is selected from α, β and γ-cyclodextrin and cyclodextrins modified with alkyl-, hydroxyalkyl-, dialkyl-, and sulfoalkyl-ether modified cyclodextrins such as methyl or hydroxypropyl β-cyclodextrins (HPβCD), sulfoalkylether-substituted beta-cyclodextrin, sulfobutylether-β-cyclodextrin (SBECD).

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/054308

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00 Version=2016.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Patseer, IPO Internal Database and Key words:Levothyroxine,cyclodextrin, amino acids,any metal iodide.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 2004060353 A1 (PHARMACIA CORPORATION) 22 Jul 2004 (22.07.2004) WHOLE DOCUMENT | 1-6 |
| Y | WO 2011104625 A1 (SUPRATEK PHARMA) 1 Sep 2011 (01.09.2011) DISCRIBTION AND CLAIMS | 1-6 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 25-11-2016 | 25-11-2016 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| Indian Patent Office<br>Plot No.32, Sector 14,Dwarka,New Delhi-110075 | D Anjaiah Nayak |
| Facsimile No. | Telephone No. +91-1125300200 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IB2016/054308

| Citation | Pub.Date | Family | Pub.Date |
|---|---|---|---|
| WO 2004060353 A1 | 22-07-2004 | CA 2509261 A1 | 22-07-2004 |
| | | EP 1575564 A1 | 21-09-2005 |
| WO 2011104625 A1 | 01-09-2011 | US 20110207764 A1 | 25-08-2011 |