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RESEARCH**

APPLICATION NUMBER:

206977Orig1s000

NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206977
Supporting document/s:	1
Applicant's letter date:	2/26/2016
CDER stamp date:	2/26/2016
Product:	Tirosint-SOL (levothyroxine sodium) oral solution of 13 mcg/mL, 25 mcg/mL, 50 mcg/mL, 75 mcg/mL, 88 mcg/mL, 100 mcg/mL, 112 mcg/mL, 125 mcg/mL, 137 mcg/mL, 150 mcg/mL, 175 mcg/mL and 200 mcg/mL
Indication:	Hypothyroidism and/or pituitary thyrotropin stimulating hormone suppression
Applicant:	Institut Biochimique SA (IBSA)
Review Division:	Division of Metabolism and Endocrinology Products
Reviewer:	Parvaneh Espandiari, Ph.D.
Supervisor/Team Leader:	C. Lee Elmore, Ph.D.
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Disclaimer

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1 Executive Summary

1.1 Introduction

Institut Biochimique SA, or IBSA (hereafter referred to as the Applicant), is seeking marketing approval of Tirosint-SOL (hereafter referred to as levothyroxine oral solution) in unit-dose ampules containing up to 200 mcg of levothyroxine sodium in (b) (4) % glycerol for the treatment of hypothyroidism and/or pituitary thyrotropin stimulating hormone (TSH) suppression as a 505(b)(2) new drug application. The drug substance levothyroxine is a synthetic thyroid hormone, but is chemically identical to the levo isomer of endogenous thyroxine (T₄). Currently, oral tablets and capsules are commercially available, but no oral solution formulations of levothyroxine are approved in the U.S.

1.2 Brief Discussion of Nonclinical Findings

No animal studies were conducted to support this 505(b)(2) marketing application for levothyroxine oral solution.

Instead, the Applicant seeks to rely upon the Agency's previous findings of safety and effectiveness for the approved Orange-book listed drugs TIROSENT[®], IBSA (NDA 021924, levothyroxine sodium capsules) and SYNTHROID[®], Abbott Laboratories (NDA 021402, levothyroxine sodium tablets). To establish a scientific "bridge" between the Applicant's levothyroxine oral solution and the listed drug TIROSENT[®] capsules (NDA 021924), the Applicant conducted one bioavailability clinical study to compare the pharmacokinetics and establish bioequivalence of the two formulations. NDA 021402 was referenced only for pediatric information.

The safety profiles of both the active ingredient (levothyroxine) and the inactive ingredient (glycerol) of levothyroxine oral solution are well established. The most common finding with levothyroxine in healthy animals and animals with compromised thyroid-status via different routes (e.g., intraperitoneal, subcutaneous, oral, or intravenous) is hyperthyroidism, an exaggerated pharmacologic response resulting in weight loss, increased food consumption, increased heart rate, increased blood pressure, and other effects. The undesired effects of levothyroxine are generally clinically monitorable and reversible in an adequately managed clinical setting.

Impurities and extractable/leachables identified were within established acceptable limits.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of levothyroxine oral solution.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Pharm/tox suggested the following deletion in product labeling:

(b) (4)

2 Drug Information

2.1 Drug

Drug Name: Levothyroxine oral solution

CAS Registry Number: 6106-07-6

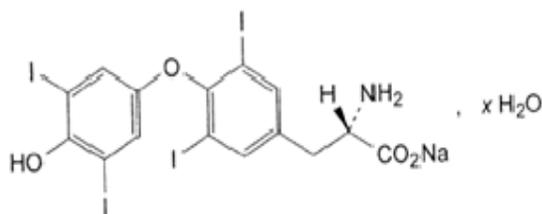
Generic Name: Levothyroxine sodium

Chemical Name (CAS): Levothyroxine (T_4) sodium [L-3,3',5,5'-tetraiodothyronine sodium salt]; sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl] propanoate; L-3,3',5,5'-tetraiodothyronine, sodium salt, pentahydrate; O-(4-hydroxy-3,5-diiodophenyl)-3,5 diiodo-L-thyronine, sodium salt, pentahydrate; L-tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt, hydrate; 3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]-L-alanine, sodium salt, pentahydrate; sodium-L- α -amino- β -[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]-propionate, pentahydrate.

Other Nonproprietary Names(s): L- T_4 Na; L-Thyroxine sodium; Monosodium L-Thyroxine hydrate

Molecular Formula/Molecular Weight: $C_{15}H_{10}I_4NNaO_4 \cdot x H_2O$ (where $x = 5$); 798.86 g/mol (anhydrous)

Structure or Biochemical Description:



Pharmacologic Class: L-thyroxine (T_4)

2.2 Relevant INDs, NDAs, BLAs and DMFs:

- IND 115023: Tirosint SOL (oral solution)
- NDA 021210: Unithroid (tablet)
- NDA 021116: Levothroid (tablet)

- NDA 021301: Levoxyl (tablet)
- NDA 021342: LEVO-T (tablet)
- NDA 021402: Synthroid (tablet)
- NDA 021924: Tirosint (capsule)
- DMF (b) (4): Levothyroxine sodium

2.3 Drug Formulation

Levothyroxine oral solution (Tirosint-SOL) is a liquid formulation of 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 mcg/mL of levothyroxine sodium in (b) (4) % glycerol. Glycerol has been used in approved drugs and it is generally recognized as safe (GRAS) by FDA (per 21 CFR 182.1320) by the oral route when produced under good manufacturing practices.

Table 1: Tirosint-SOL composition (Applicant's Table):

Component Name	Quantity/mL	Function	Reference
Drug Substance			
Levothyroxine Sodium			
13 µg	0.013 mg	Active Ingredient	USP current edition
25 µg	0.025 mg		
50 µg	0.050 mg		
75 µg	0.075 mg		
88 µg	0.088 mg		
100 µg	0.100 mg		
112 µg	0.112 mg		
125 µg	0.125 mg		
137 µg	0.137 mg		
150 µg	0.150 mg		
175 µg	0.175 mg		
200 µg	0.200 mg		
Excipient			
Glycerol (b) (4)		(b) (4)	EP/USP current edition

2.4 Comments on Novel Excipients

There are no novel excipients in the drug formulation.

2.5 Comments on Impurities/Degradants of Concern

The Applicant reported the impurity profile of the drug substance is consistent with the acceptance criteria described in the USP monograph of Levothyroxine sodium.

Table 2: Impurity Profile (Applicant's Table)

Impurity	USP Acceptance Criteria
	(b) (4)
Triiodothyroacetic acid	≤ 0.15%
	(b) (4)
O-(4-hydroxy-3,5-diiodophenyl)-thyroxine	≤ 0.50%
O-methyl-tetraiodothyroethylamine	≤ 0.30%
Levothyroxine-N-methylamide	≤ 0.15%
Any other unspecified impurity (largest)	≤ 0.10%
Total impurities	≤ 2.0%
	(b) (4)

Table 3: Drug Product Specifications (Applicant's Table)

Test	Acceptance Criteria	Method
Appearance	Clear, colorless to slightly yellow solution	Visual Inspection (b) (4)
Uniformity of Dosage Units (Weight Variation) *		
Levothyroxine Sodium Identification	Positive	HPLC
Levothyroxine Sodium Assay	(b) (4) % of labeled amount	HPLC
Impurities / Degradation Products:		
- Single Unknown Impurity	(b) (4)	HPLC
- Total Impurities	(b) (4)	
Seal Test§: - Strip - Over-Pouch	No leakage is observed No blue solution is observed inside the over-pouch	Visual Inspection
Microbial Control: - Total Aerobic Microbial Count - Total Yeasts and Molds Count - <i>Escherichia coli</i>	(b) (4) Colony Forming Unit (CFU)/g (b) (4) CFU/g Absent/g	USP <61> USP <62>
	(b) (4)	

In addition, the following extractable substances were reported for the drug product container from analytical studies: (b) (4)

Amounts of all these leachable substances were within acceptable limits based on ICH Q3A and Q3B qualification thresholds and the limits recommended by the Product Quality Research Institute (PQRI). See the table below for more information related to these impurities:

Table 4: Extractable Substances: Leachables



(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Levothyroxine oral solution presentations include 12 dosage strengths (13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 mcg/mL). Levothyroxine oral solution will be administered as a single daily dose, and it will be individualized and adjusted based on replacement or suppressive therapy requirements.

2.7.1 Regulatory Background

- Pre-IND written responses were conveyed to the Sponsor for IND 115023 on 27 June 2012 regarding the development program for the levothyroxine oral solution. The Agency did not request any nonclinical studies.
- On 9 September 2012, the Applicant proposed a clinical study protocol designed to demonstrate that the relative bioavailability and safety of levothyroxine oral solution is comparable to TIROSINT® capsules (NDA 021924) following a single oral dose of 600 mcg in healthy subjects under fasting condition.

- On 20 June 2013, a pre-NDA meeting was held under IND 115023 to discuss the adequacy of the development program for levothyroxine oral solution in patients requiring levothyroxine replacement therapy or pituitary TSH suppression to support a 505(b)(2) new drug application.

3 Studies Submitted:

No nonclinical studies were submitted.

3.3 Previous Reviews Referenced

A Pharm/Tox review was submitted to IND 115023 (DARRTS; 10 October 2012), which supported the clinical bioequivalence study.

4 Pharmacology

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxin (T_4). In the body, T_4 is secreted by the follicular cells of the thyroid. Synthetic T_4 is identical to the endogenous hormone produced by the human thyroid gland. T_4 is converted to T_3 in the liver and kidney. In general, the primary functions of thyroid hormones (T_3 and T_4), upon binding to nuclear thyroid binding receptors, are to increase cardiac function and the basal metabolic rate, regulate growth and development, and affect a broad range of other vital metabolic processes.

4.2 Secondary Pharmacology

No secondary pharmacology studies were required.

4.3 Safety Pharmacology

No safety pharmacology studies were required.

5 Pharmacokinetics/ADME/Toxicokinetics

No additional studies were required.

Pharmacokinetic drug interactions:

No studies were conducted to assess the potential for drug-drug interactions.

5.2 Toxicokinetics

6 General Toxicology

6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies were conducted by the Applicant with levothyroxine oral solution.

Toxicities observed in animals with other levothyroxine formulations are exaggerated pharmacological effects due to the excess thyroid hormone activity in euthyroid animals. These effects include decreased body weight, increased body temperature, cardiac

hypertrophy (increased heart mass, heart rate, and ion channel changes), decreased bone mineral density and increased LFTs.

7 Genetic Toxicology

No genotoxicity studies were conducted.

8 Carcinogenicity

No carcinogenicity studies were conducted. Synthetic T₄, the levo isomer of thyroxine, is chemically identical to thyroxine produced by the human thyroid gland.

9 Reproductive and Developmental Toxicology

No reproductive studies were conducted by the Applicant with levothyroxine sodium.

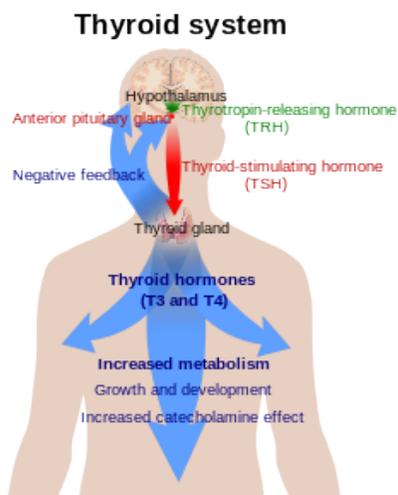
It is generally known that maternal thyroid hormones do not readily cross the placenta into the fetal circulation, and clinical experience does not indicate any adverse effect on the fetus when thyroid agents are administered during pregnancy.

11 Integrated Summary and Safety Evaluation

The Applicant seeks approval for levothyroxine oral solution at up to 200 mcg of levothyroxine sodium in glycerol for treatment of hypothyroidism and/or pituitary thyrotropin stimulating hormone (TSH) suppression as a 505(b)(2) application.

No animal studies were submitted to support the marketing application for levothyroxine oral solution. Instead, the Applicant relies on the Agency's previous findings of safety and effectiveness for previously approved product TIROSINT® (levothyroxine sodium capsules, NDA 021924), and a clinical bioavailability study comparing the pharmacokinetics of the two formulations.

In the body, thyroid hormone (T₄ and T₃) synthesis and secretion is regulated by the hypothalamic pituitary-thyroid axis (see figure, below):



(https://en.wikipedia.org/wiki/Thyrotropin-releasing_hormone)

In general, production of thyroid hormone is increased by thyroid-releasing and thyroid-stimulating hormones, while thyroid hormone suppresses secretion of thyroid-releasing and thyroid-stimulating hormones in a classical negative feedback loop. The pharmacologic effects of thyroid hormones are well known and impact a broad array of physiological functions, including the basal metabolic rate of the body, effects on protein synthesis, regulation of bone growth, augmentation of neural maturation, and the regulation of cell growth and differentiation.

Levothyroxine oral solution consists of the active pharmaceutical ingredient, levothyroxine sodium (synthetic T₄), and the inactive ingredient, glycerol. The pharmacologic and safety profiles of the active ingredient, levothyroxine, have been established in animals, as well as in humans where there is long-standing precedent for replacement hormone therapy for reduced or absent thyroid gland/function. The most common findings with administration of levothyroxine to healthy animals and those with compromised thyroid function are those associated with an exaggerated pharmacologic response to excess thyroid hormone (i.e., thyrotoxicosis), characterized by weight loss, increased food consumption, elevated heart rate, higher blood pressure, etc.

Orally administered levothyroxine sodium tablets were marketed previously, but were approved as early as 2002 as thyroid function replacement for the cretinism, myxedema, non-toxic goiter, and/or hypothyroidism. The proposed oral solution of levothyroxine is approved in Europe for the treatment of hypothyroidism, diffuse nontoxic goiter or Hashimoto's thyroiditis, and thyroid carcinoma. Adverse effects of levothyroxine (i.e., hyperthyroidism-related effects) are generally monitorable and reversible in a well-managed clinical setting.

The mutagenic or carcinogenic potential of levothyroxine sodium has not been evaluated with animal studies, since the synthetic hormone is identical to the endogenous hormone. No animal studies have been conducted to determine the effect of levothyroxine on fertility or reproduction. Hypothyroidism is detrimental to human reproduction.

There are no safety concerns regarding the inactive ingredient, glycerol. Glycerol is common in approved drugs and is generally recognized as safe by FDA (21 CFR 182.1320) by the oral route in accordance with good manufacturing practice.

The drug product's impurity profile appears acceptable, based on compendial (USP) drug substance/product specifications and evaluation procedures. The levels of container leachables identified were evaluated and determined to be within acceptable limits.

There are no nonclinical safety concerns regarding the use of levothyroxine oral solution based on available data that should preclude approval of this application.

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/s/

PARVANEH ESPANDIARI
11/04/2016

CALVIN L ELMORE
11/07/2016
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Numbers: 206977	Applicant: Institut Biochimique SA (IBSA)	Stamp Date: 2/26/2016
Drug Name: Tirosint-SOL (levothyroxine sodium oral solution)	NDA Type: 505(b)(2)	

On initial overview of the NDA application for filing:

NDA 206977 was submitted as 505(b)(2) application for Tirosint-SOL (oral solution containing up to 200 µg of levothyroxine sodium in glycerol (b)(4)%) for treatment of hypothyroidism and/or pituitary thyrotropin stimulating hormone (TSH) Suppression.

To support this application, the Applicant is relying on FDA’s finding of safety and effectiveness for approved listed drug (LD) Tirosint® (NDA 021924). Both formulations (applicant’s Tirosint SOL and LD, Tirosint) have the same active ingredient. The Applicant submitted a “bridge” clinical bioequivalence study between these two formulations as well as provided cross references to: NDA 021402 (SYNTHROID®, Abbott Laboratories); NDA 021924 (TIROSINT®, IBSA); IND 115023 (Tirosint®-SOL, IBSA); and DMF Type II (b)(4) of Levothyroxine Sodium, (b)(4)

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The EDR submission has 5 modules – regional, common technical document summary, quality, nonclinical study reports, and clinical study reports.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		To support 505(b)(2) application, the Applicant is relying on FDA’s finding of safety and effectiveness for approved LD (Tirosint®, NDA 021924). To establish a “bridge” between these two formulations (the applicant’s formulation and the LD formulation), a clinical bioequivalence study was conducted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A; no nonclinical studies were submitted.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A; no nonclinical studies were submitted.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A; no nonclinical studies were submitted.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A; no nonclinical studies were submitted.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		The labeling draft has information from previous approved NDA with PLLR requirement.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A; no abuse potential issues have been identified.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A; no abuse potential issues have been identified.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

No review issues for the 74-day letter.

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/s/

PARVANEH ESPANDIARI
04/13/2016

CALVIN L ELMORE
04/13/2016