

Cross-Discipline Team Leader Review

Date	12/5/2016
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 206977
Supplement#	
Applicant	Institut Biochimique SA (IBSA)
Date of Submission	February 26, 2016
PDUFA Goal Date	December 26, 2016
Proprietary Name / Established (USAN) names	Tirosint-SOL/Levothyroxine sodium
Dosage forms / Strength	Oral solution: 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, 200 mcg/ml.
Proposed Indication(s)	1) hypothyroidism - as replacement therapy in congenital or acquired hypothyroidism; 2) pituitary thyrotropin-stimulating hormone (TSH) suppression - as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer. (b) (4)
Recommended:	Approval

1. Introduction

On February 26, 2016 Institut Biochimique SA (IBSA) submitted this 505(b)(2) new drug application for Tirosint-SOL (levothyroxine sodium oral solution; LSOS) at doses 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, 175 mcg/ml, 200 mcg/ml seeking approval for treatment of hypothyroidism and pituitary TSH suppression. The Sponsor relies on FDA's previous findings of safety and effectiveness for the reference drugs, Tirosint (levothyroxine sodium capsules, NDA 021924; for doses between 13 mcg and 150 mcg), and Synthroid (levothyroxine sodium tablets, NDA 021402; for doses between 175 mcg and 200 mcg and for pediatric patients under six years old) that are approved for the same indications.

The Sponsor currently markets Tirosint capsules (NDA 021924, approved in 2006, for doses between 25 mcg and 150 mcg, and NDA 022121, approved in 2007, for dose 13 mcg). NDAs for Tirosint capsules were approved under Section 505 (b)(2) of the Food, Drug, and Cosmetics Act.

Current approved oral levothyroxine sodium products include Synthroid (NDA 21402), Levoxyl (NDA 21301), Levo-T (NDA 21342), Tirosint (NDA 021924 and 022121), Novothyrox (NDA 21292), Unithroid (NDA 21210), Levolet (NDA 21137), Thyro-Tabs

(NDA 21116) and generics. All oral levothyroxine sodium products are available in tablet form or capsule form; no oral solution dosage form of levothyroxine is approved in the US.

As per the Sponsor, the expected advantage of an oral solution compared to a solid oral formulation of levothyroxine is the ease of administration, in particular, to patients who have difficulties or are not able to swallow intact capsules or tablets (including small children).

To support the approval of Tirosint-SOL for the proposed indications, the Sponsor submitted study 14016, a randomized, open-label, 3-way cross-over, comparative bioavailability study of levothyroxine sodium oral solution (test product) administered with and without water and Tirosint capsules 150 mcg (a reference drug) following an oral administration of a 600 mcg single dose in healthy adults volunteers under fasting conditions.

2. Background

The major regulatory interactions between the Sponsor and the Division were summarized by the chemistry, manufacturing and controls team (CMC) and the clinical pharmacology team (refer to CMC review from 11/10/2016, Clinical Pharmacology review from 10/4/2016 and to Division's Meeting Comments from 4/2/2012, 7/2012, 11/7/2012, 7/3/2013 and Division's correspondences via email from 7/2012, 9/2013, 11/2015, 1/2016).

Briefly,

1) PIND meeting (4/2/2012)

This meeting set the overall direction of the levothyroxine sodium oral solution development program. The Agency provided overall guidance on submission of 505(b)(2) NDA. The Agency also indicated that "since IBSA is the applicant for both Levothyroxine sodium oral solution and Tirosint, you [the Sponsor] must re-certify to the listed drug (i.e. Synthroid) relied-upon in the Tirosint application".

The Agency also recommended using the 150 mcg strength in BE study because it is listed as the reference listed drug product in the Orange Book.

Lastly, the Agency agreed to waive the requirement for a dose-proportionality study if the biowaiver request is included as part of the NDA submission and there are bioavailability/bioequivalence (BA/BE) data for the highest strength tested clinically of the proposed drug product.

2) The Sponsor requested further clarification regarding the levothyroxine formulation to be used in BE study (6/28/2012).

FDA provided the responses via email on 7/25/2012 clarifying the use of Tirosint and Synthroid as reference drugs in 505(b)(2) NDA and as the comparators in BE study. In particular, the Agency indicated that "since Tirosint is the Sponsor's own product, [the Sponsor] will be referencing the data in it, rather than relying upon it, so no certification will be needed. As a piggyback (b)(2), [the Sponsor] must list Synthroid as a listed drug".

The Agency also indicated that the Sponsor can use any drug (Synthroid or Tirosint) as a comparator in the BE study, however, if Tirosint will be used, the Sponsor does not need to re-bridge to Synthroid (if Synthroid will be used, the Sponsor might need to bridge to Tirosint depending on what information in Tirosint is being referenced).

3) IND 115023 was opened on 9/24/2012 with a protocol for a randomized, open-label, 2-way crossover comparative bioavailability study of levothyroxine sodium oral solution (test) and Tirosint Capsules (reference) following a single oral dose of 600 mcg in healthy subjects under fasting conditions. The study was allowed to be proceeded. Of note, the proposed levothyroxine sodium oral solution (test) for this study (b) (4).

4) PNDA meeting (6/20/2013)

During this meeting, the Division raised a concern that the proposed levothyroxine formulation (b) (4) and still proposed to be used in small children. The Agency indicated that if the Sponsor decides to reformulate the drug (b) (4), a new BE study would be needed. The Agency also recommended evaluating the effect of water on the oral solution in case of reformulation of the product.

5) The Sponsor agreed to reformulate levothyroxine sodium oral solution using only (b) (4) glycerol (b) (4). CMC found the Sponsor's proposal to be acceptable (email from 9/12/2013). The Sponsor also agreed to conduct a new BE study using (b) (4) levothyroxine oral solution formulation administered with and without water (Annual Report 2, submitted on 10/28/2014 in DARRTS).

6) NDA submission: 2/26/2016.

3. CMC/Device

The CMC reviewers recommend approval of this supplement (refer to Dr.'s Tran executive summary from 11/10/2016). There is no outstanding issue that precludes approval.

All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance have determined that these facilities are acceptable. DMF (b) (4) by (b) (4) is referenced for all CMC information on the drug substance. CMC reviewers found DMF (b) (4) to be adequate.

Tirosint-SOL is manufactured as an oral solution. Tirosint-SOL presentation is an ampule containing 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 mcg/ml of levothyroxine sodium (b) (4) in (b) (4) glycerol USP (b) (4).

CMC reviewers concluded that all regulatory drug product specification including attributes standard for this type of dosage form are acceptable. Refer to CMC review for details.

The container closure system (white opaque LDPE (b) (4) unit-dose ampules with a protective (b) (4) pouch as secondary packaging) was found to be adequate. LDPE extractables and leachables studies were conducted and the identified leachable content was significantly below the PQRI qualification threshold of 150 mcg/day. No issues on CC system that would preclude approval were identified.

An expiry of 18 months was granted when stored at room temperature, (b) (4)

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical pharmacology/toxicology studies in this application.

As per Pharmacology/ Toxicology reviewers, impurities and extractable/leachables identified are within established acceptable limits and the safety profiles of both the active ingredient (levothyroxine) and the inactive ingredient (glycerol) of levothyroxine oral solution are well established.

Dr. Parvaneh Espandiar and pharmacology/toxicology supervisor, Dr. C. Lee Elmore, recommended approval of Tirosint-SOL (refer to review in DARRTS from 11/07/2016). I concur with Drs. Espandiar's and Elmore's assessment that there are no nonclinical pharmacology/toxicology issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Biopharmaceutics

The Sponsor requested a biowaiver for strengths that were not studied in pivotal BE study 140161. Namely, 13, 25, 50, 75, 88, 100, 125 and 137 mcg/ml (lower strengths) and 175 mcg and 200 mcg/ml (higher strengths).

The biopharmaceutics team (refer to Biopharmaceutics review from 9/28/2016 for details) concluded that:

- 1) Comparative dissolution data are not required because Tirosint-SOL is an oral solution
- 2) The different strengths of the proposed oral solution are considered to be proportionally similar, because: a) the drug product is an oral solution without any other excipients other than 85% of glycerol, which contributes to the whole weight of the oral solution; and b) the concentration of the active ingredient is very low, and it is less than 0.02% of the total weight of the oral solution even in the highest strength of 200 mcg /mL
- 3) The dosage form proportionality study is not required to support the biowaiver request for this drug product because the proposed drug product is an oral solution, and levothyroxine is absorbed from the solution instantly.

Lastly, as it was discussed between the Agency and the Sponsor during multiple communications, the Agency agreed to waive the requirement for a dose-proportionality study if "there are BA/BE data for the highest strength tested clinically of your proposed drug product" (PIND meeting minutes from 6/27/2012 in DARRTS) and "biowaiver... for the 175 and 200 mcg/ml dosage strengths can be granted based on demonstration (b) (4) different strengths and linear PK of the drug substance across the entire range" (Agency's response to Information Request via email from September 25-29, 2013). Biopharmaceutics reviewer reviewed the information submitted in this NDA to support waiver request and concluded that 1) "for the listed drug product for the proposed oral solution, Tirosint tablet (NDA 021924), the highest approved strength is 150 mcg. Therefore, it is reasonable that the Applicant used 150 mcg strength in clinical BE study of 600 mcg total dose; and 2) "PK linearity is not required for waiver of higher strength of levothyroxine ..., since clinical PK study with different strengths (including the highest strength 200 µg/mL of levothyroxine) has to be conducted with the same pharmacological dose of 600 µg, in order to measure changes of serum concentrations against the background of endogenous T4"

Thus, the requested waiver was granted by the biopharmaceutics team on 9/28/2016.

Clinical Pharmacology

The Sponsor’s submission included the results of the three BE studies:

- Study 130284 is a 3-way crossover relative bioavailability study of levothyroxine sodium oral solution (test) administered with and without water and Tirosint capsule (reference) following a single oral dose of 600 µg under fasting in healthy volunteers.
- Study 140143 is a pilot 3-way crossover relative bioavailability study evaluating the rate and extent of absorption of 150 µg dosage strength levothyroxine sodium oral solution compared to 150 µg Tirosint capsules and 100 µg unit-dose ampules of the prototype (b) (4) formulation of levothyroxine sodium oral solution following a single oral dose of 600 µg under fasting in healthy volunteers.
- Study 140161 is a pivotal 3-way crossover relative bioavailability study of levothyroxine sodium oral solution (test) administered with and without water and Tirosint capsule (reference) following a single oral dose of 600 µg under fasting in healthy volunteers.

The results of two studies, study 130284 and study 140143, were not reviewed by clinical pharmacology team because study 130284 failed to demonstrate BE between Tirosint-SOL and Tirosint capsule due to the incomplete dosing with liquid formulation (incomplete emptying of the ampules) and study 140143 used e (b) (4) levothyroxine liquid formulation (the to-be marketed Tirosint-SOL contains glycerol only).

The results of pivotal study 140161 and conclusions are briefly summarized below (refer for details to Clin.Pharm review in DARRTS from 11/07/2016).

Dr. Lau independently verified the Sponsor’s results for the analysis that included all participants data and concluded that BE study demonstrated BE between Tirosint-SOL and Tirosint Capsule based on corrected and uncorrected PK levothyroxine parameters because “90% CIs of levothyroxine AUC and Cmax geometric mean ratios (GMR) were within the 80 and 125% BE goalpost” (Table 1). Dr. Lau also repeated the analysis excluding one patient who did not received all assigned treatments. The results of the second analysis still demonstrated BE between Tirosint-SOL and Tirosint Capsule.

Table 1. Statistical comparison of levothyroxine parameters between the reviewer’s analyses and the Sponsor analysis.

Test (Tirosint-SOL)	Reference (Tirosint capsule)	Parameter	Reviewer’s and Sponsor’s analysis including data from all participants, (n=36)		Reviewer’s analysis excluding data from one participant, (n=35)	
			GMR	90% CI	GMR	90% CI
Baseline corrected levothyroxine PK parameters						
1	3	AUC ₀₋₄₈ , ng.hr/ml	98.5	94.8-102.1	98.5	90.6-107.1
1	3	C _{max} , ng/ml	95.3	92.0-98.8	95.3	92.0-98.8
2	3	AUC ₀₋₄₈ , ng.hr/ml	101.2	97.4-105.0	95.7	87.8-104.3
2	3	C _{max} , ng/ml	94.6	91.2-98.2	94.8	91.4-98.3
Baseline uncorrected levothyroxine PK parameters						
1	3	AUC ₀₋₄₈ , ng.hr/ml	99.9	98.3-101.6	99.9	91.5-109.1
1	3	C _{max} , ng/ml	97.7	95.6-99.9	97.7	95.6-99.8
2	3	AUC ₀₋₄₈ , ng.hr/ml	99.8	98.2-101.5	93.7	85.7-102.5
2	3	C _{max} , ng/ml	96.5	94.5-98.9	96.7	94.6-98.9

Treatment 1= Tirosint-SOL with water; Treatment 2 = Tirosint-SOL without water; Treatment3= Tirosint capsule. Source: Clin.Pharm reviewer's tables 3 and 4, modified.

Overall, the clinical pharmacology reviewers concluded that the results of the study established BE between Tirosint-SOL and Tirosint Capsule and recommended approval of this NDA. I concur with Dr. Lau and Dr. Vaidyanathan recommendations.

6. Clinical Microbiology

No new data in this application

7. Clinical/Statistical- Efficacy

There are no new clinical efficacy data essential for the risk/benefit assessment of Tirosint-Sol.

8. Safety

There are no new clinical safety data essential for the risk/benefit assessment of Tirosint-SOL.

The Sponsor submitted supportive safety data from three BE studies conducted in healthy volunteers. The safety findings were reviewed by Dr. Sharretts; please refer to his clinical review for details. No death or SAEs were recorded in three studies. The most common adverse events were headache and somnolence.

Dr. Sharretts concluded that safety profile of Tirosint-SOL was consistent with the known safety profile of approved levothyroxine formulations. I agree with Dr. Sharretts' conclusions that the submitted data did not identify any new safety issues.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

10. Pediatrics

No pediatric patients were studied as part of the Tirosint-SOL development program. The Division and the Pediatric Review Committee agreed that no additional pediatric studies were needed because this product is appropriately labeled for use in all relevant pediatric populations (11/ 2/2016).

11. Other Relevant Regulatory Issues

OSIS inspection

- Office of Study Integrity and Surveillance (OSIS) recommended to accept the data without an on-site inspection because the OSIS recently inspected the sites and found No Action to be Indicated (DARRTS, 8/8/2016) at these sites.

Financial Disclosure

FDA 3453 form was submitted confirming that the applicant of the submitted studies did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trials (refer to Dr. Sharretts' review).

12. Labeling

Proprietary name

The proposed proprietary name for levothyroxine oral solution is Tirosint-SOL. This was reviewed and deemed acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on May 23, 2016.

Labeling

At the time of this memorandum, the label was undergoing revisions following input from all disciplines. Additional labeling changes which I would recommend include modification of the indication language (i.e. removal of the [REDACTED] (b) (4) from indication) and adding Limitations of Use to Indication and Usage section (section 1) of the label. Limitation of Use section should indicate that Tirosint-Sol is not indicated for suppression of benign thyroid nodules and goiter and not indicated for treatment of hypothyroidism due to thyroiditis.

Agreement on the final labeling language has not been reached at the time this review was completed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
Approval.

- Risk Benefit Assessment
The evidence provided in this application supports the approval of Tirosint-SOL for treatment of hypothyroidism and TSH suppression indications because: 1) the Sponsor established that PK/PD of Tirosint-SOL is bioequivalent to the reference drugs, Synthroid tablets and Tirosint Capsules; 2) Synthroid and Tirosint capsules were previously determined to be safe and effective for the same indications. Thus, it is expected that the benefits and risks of Tirosint-SOL use at proposed doses will be similar to the benefits and risks of reference drugs (Tirosint Capsule and Synthroid) in patients with hypothyroidism and in those who require pituitary TSH suppression.

Safety profile of Tirosint-SOL is consistent with the known safety profile of approved levothyroxine formulations and no new safety signals were identified in this NDA.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

- Recommendation for other Postmarketing Requirements and Commitments
None

- Recommended Comments to Applicant
None

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/s/

MARINA ZEMSKOVA
12/05/2016

JEAN-MARC P GUETTIER
12/05/2016

Dr. Zemskova's review serves as the summary basis for approval. I concur with her recommendation to approve this NDA.