CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206977Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 206977
Review #1
Review Date (see last page)

Drug Name/Dosage Form	levothyroxine sodium oral solution
Strength	13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 mcg/mL
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Institut Biochimique SA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0001	2/26/16
0005	6/20/16
0007	8/10/16
0008	8/18/16

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
API	Jeffrey Medwid	New Drug API/ONDP
Drug Product	Elise Luong	New Drug Products II/ONDP
Process	Erin Kim	Process Assessment II/OPF
Facility	Donald Lech	Inspectional Assessment/OPF
Biopharmaceutics	Vincent Duan	Biopharmaceutics/ONDP
Microbiology	Julie Nemecek	Process Assessment II/OPF

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	levothyroxine Na	Adequate	11/3/14	see last page of API/drug substance review

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21924	TIROSINT (levothyroxine sodium capsule) Same applicant

2. CONSULTS: not applicable

Executive Summary

I. Recommendation and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the Manufacturing and Testing Facilities Recommendation) is for **APPROVAL**.

II. Summary of Quality Assessment

A. Product Overview

This is a 505(b)(2) application that relies on the applicant's approved NDA 21924 Tirosint Capsules (same drug substance), which is a 505(b)(2) application that relies on FDA's findings of safety and effectiveness for the listed drug Synthroid Tablets of NDA 21402.

One pivotal comparative bioavailability study was conducted to establish BE of the 150 mcg strength of the new product (batch 140701) and Tirosint. The biobatch has the commercial formulation and was manufactured at the commercial site and batch size, using the commercial process. A supportive BE study was conducted using another batch of the 150 mcg strength of the new product (batch 130802) to compare the product to Tirosint [redacted] (b) (4) formulation; this batch 103802 is also one of the primary stability batches. A biowaiver is granted for all other dosage strengths based on their being compositionally proportional. Dosage-form proportionality and comparative dissolution are not required to support the biowaiver because the drug product is an oral solution and the active ingredient has instant absorption.

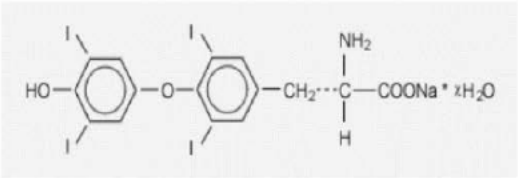
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	chronic
Maximum Daily Dose	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	not applicable

B. Quality Assessment Overview

Drug Substance

Chemical Name or IUPAC Name/Structure:

TIROSINT-SOL (levothyroxine sodium) is L-thyroxine. The orally-administered solution contains synthetic L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T_4 is chemically identical to that produced in the human thyroid gland. Levothyroxine (T_4) sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \cdot x\ H_2O$ (where x = 5), molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



DMF (b) (4) by (b) (4) is referenced for all CMC information on the drug substance levothyroxine sodium. The DMF is currently adequate.

Drug Product

The product is an oral solution with the dosage strengths of 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 mcg/mL, dissolved in (b) (4)% glycerol USP.

The drug substance is formulated in (b) (4)% glycerol to optimize both solubility and stability. Solubility in lower concentrations of glycerol was found to be less adequate, and significant degradation was found for the (b) (4)% glycerol formulation. (b) (4) Compatibility of the product when mixed with water, which is described in the Dosage and Administration section of the prescribing information, was demonstrated adequate by clinical outcome (the same procedure was used in the clinical studies, and the diluted product is labeled for immediate administration).

The product manufacturing process consists of dissolution of the drug substance in (b) (4)% glycerol (b) (4)

The regulatory drug product specification includes attributes standard for this type of dosage form, including microbial tests and limits.

Each single-dose ampule contains (b) (4) 1mL solution. The limit of (b) (4)% on an unidentified degradant (b) (4) Only one degradant is specified: (b) (4) The proposed limit of (b) (4)% on (b) (4) for the (b) (4)

Container Closure: White opaque LDPE semi-permeable unit-dose ampules with a protective (b) (4) pouch as secondary packaging.

Both the LDPE and colorant components complies with the indirect food additive regulations. LDPE extractables and leachables studies were conducted, and the identified leachables content is significantly below the PQRI qualification threshold of 150 mcg/day.

Expiration Date & Storage Conditions: 18 months at room temperature (excursions permitted to 15-30 C) (b) (4)

Stability data include three batches of the lowest and highest strengths (13 and 200 mcg) and one batch each of the other strengths. All batches have the commercial formulation and were manufactured at (b) (4) ampules/batch (commercial scale) or (b) (4) ampules/batch, by the

commercial process and site, and packaged in the in a container closure system similar to the commercial system (only difference is a non-product-contact part to be used for labeling) including the pouch secondary packaging. No in-use stability data for the producted diluted in water is required because the instruction is for immediate administration (no in-use storage).

C. **Special Product Quality Labeling Recommendation**: not applicable
D. **Life Cycle Knowledge Information/ Final Risk Assessment:** page 29 of Drug Product review, page 16 of Process review, last page of Microbiology review

Application Technical Lead Signature:

Suong (Su) Tran, Ph.D.
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CHAPTERS: Primary Quality Assessment

Chapter I: Drug Substance
Chaper II: Drug Product
Chapter III: Environmental Assessment
Chapter IV: Labeling
Chapter V: Process
Chapter VI: Facilities
Chapter VII: Biopharmaceutics
Chapter VIII: Microbiology
Attachment I: Final Risk Assessment (see last page of Executive Summary)

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 206977

Drug Product Name / Strength: Tirosint-SOL (levothyroxine sodium) oral solution

Route of Administration: Oral

Applicant Name: Institut Biochimique SA (IBSA)

Indication: Hypothroidism and pituitary thyrotropin stimulating hormones (TSH) suppression

Review Summary:

The proposed drug product Tirosint-SOL is an oral solution containing 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 µg of levothyroxine sodium dissolved in glycerol (b) (4)%. The composition of the proposed drug product is shown in Table 1. Tirosint–SOL is supplied in a white, non-transparent, low-density polyethylene squeezable ampule delivering a 1.0 mL dose. This is a 505b (2) submission, with reference to listed drugs Triosint (levothyroxine sodium) capsules (NDA 021924) and Synthroid tablets (NDA 021402). Since the proposed drug product is an oral solution, review on dissolution is not necessary. Biopharm review focuses on biowaiver request for lower and higher strengths.

Table 1. Composition of the proposed oral solution

Component Name	Quantity/mL	Function	Reference
Drug Substance			
Levothyroxine Sodium		Active Ingredient	United States Pharmacopeia (USP) current edition
13 µg	0.013 mg		
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)		European Pharmacopoeia (EP)/USP current edition
Total			

*Corresponding to (b) (4) of glycerin.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

{Assess method development, method robustness, and criteria; modeling approach}

The proposed drug product is an oral solution; therefore, there is no review on dissolution.

Biowaiver Request

Reviewer's Assessment:

The proposed drug product is supplied in unit dose ampules containing 13, 25, 50, 75, 88, 100, 125, 137, 150, 175 or 200 µg/mL of levothyroxine sodium dissolved in glycerol (b)(4)%. Each ampule is filled to a nominal volume of (b)(4)1 mL to assure the delivery of 1 mL. The Applicant conducted BE study (Study 140161) to compare bioavailability of 600 mcg of the proposed oral solution product in 150 mcg strength with or without water (4 x 150 mcg LSOS ampules) to 600 mcg dose of listed drug product Tirosint (4 x 150 mcg) capsules. The BE study will be reviewed by clinical pharmacology reviewer (please refer to clinical pharmacology review for additional details). For other strengths, the Applicant submitted a biowaiver request for both lower strengths (13, 25, 50, 75, 88, 100, 125, and 137 µg/mL) and higher strengths (175 and 200 µg/mL).

According to ***Guidance for Industry Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing***, levothyroxine sodium is a compound with a narrow therapeutic range. Because levothyroxine is naturally present in minute quantities in the blood, 600 mcg of total dose is recommended in the design of BE study to allow the measurement of levothyroxine sodium after a single dose.

For levothyroxine sodium tablets, in order to obtain biowaiver for other strengths, in addition to BE study with 600 mcg, a dosage-form proportionality study among the to-be-marked tablet strengths of levothyroxine sodium (low, medium, and high strengths) is required. Other requirements include compositional proportion of the tablet formulation, and comparative dissolution study of the different strengths.

The proposed drug product is an oral solution, without any other excipients other than (b)(4)% of glycerol, which almost contributes to the whole weight of the oral solution. The different strengths differ only in the amount of active ingredient. Nevertheless, the concentration of the active ingredient is very low, and it is less than (b)(4)% of the total weight of the oral solution even in the highest strength of 200 mcg /mL. As described in ***Guidance for Industry Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General***

Considerations, for high potency drug substance (where the amount of active drug substance in the dosage form is relatively low), proportional similarity is defined as:

a) The total weight of the dosage form remains nearly the same for all strengths (within ± 10 % of the total weight of the strength on which a BE was performed),

b) The same inactive ingredients are used for all strengths, and,

c) The change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.

The Applicant conducted a BE study with 150 mcg / mL strength, and the active ingredient in all other strengths is within (b)(4)% of the total weight of 150 mcg / mL strength. Glycerol is the only inactive ingredient for all strengths, and the change in any strength is achieved by altering the amount of levothyroxine while keeping the amount of glycerol the same. Since the amount of levothyroxine is less than (b)(4)% of the total weight of the oral solution even in the highest strength of 200 mcg /mL; therefore, the different strengths of the proposed oral solution are considered to be proportionally similar.

As the only excipient in the oral solution, glycerol, will not significantly affect drug absorption (as defined in 21 CFR 320.22(b) (3) (iii)), and the 150 mcg strength of the proposed oral solution drug product reached BE with the listed drug product in BE study 140161. The acceptance of the BE study will be determined by Clinical Pharmacology reviewer.

Dosage-form proportionality of levothyroxine in tablet formulation has been previously demonstrated on the listed drug (Tirosint capsules NDA 021924) and published results (Walter-Sack et al. Assessment of levothyroxine sodium bioavailability: recommendations for an approved methodology based on the pooled analysis of eight identically designed trials with 396 drug exposures. Clin Pharmacokinet 2004; 43:1037-53). Although dosage-form proportionality study is required in ***Guidance for Industry Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing***, it is for tablet formulation. While the proposed drug product is an oral solution, and levothyroxine is absorbed from the solution instantly (Clin Pharmacokinet 2004; 43:1037-53). Therefore, dosage form-proportionality study is not necessary to support the biowaiver request for this oral solution drug product. In the communication between the Agency and the Applicant for PIND meeting dated 06/27/2012, regarding the waiver of dosage-form proportionality study, following Biopharm comments were recommended:

Generally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption (21 CFR 320.22(b)(3)(iii)). We agree to waive the requirement for a dose-proportionality study if the following criteria are met:

A. The biowaiver request is included as part of the NDA submission; and

B. There are BA/BE data for the highest strength tested clinically of your proposed drug product.

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 as described in meeting minutes for Pre-NDA meeting dated July 3, 2013.

Since it is an oral solution, comparative dissolution data is not required. Furthermore, PK linearity is not required for waiver of higher strength of levothyroxine even for tablet formulation, 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 (Walter-Sack et al. Clin Pharmacokinet 2004; 43:1037-53; Berg JA, Mayor GA. J Clin Pharmacol 1993; 33:1135-40).

Overall, the biowaiver request for the lower strengths (13, 25, 50, 75, 88, 100, 125, and 137 µg/mL) and higher strengths (175 and 200 µg/mL) is acceptable. From the Biopharmaceutics perspective, NDA 206977 is recommended for approval.

List of Deficiencies:

N/A

Primary Biopharmaceutics Reviewer Name and Date: Peng (Vincent) Duan, Ph.D. 08/21/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D. 09/28/2016,

Haritha Mandula

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Date: 9/29/2016 09:47:09AM
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Peng Duan

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MICROBIOLOGY

Product Background:

NDA: 206977

Drug Product Name / Strength: Levothyroxine Sodium (oral solution), 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200µg/mL

Route of Administration: Oral solution

Applicant Name: Institut Biochimique SA (IBSA)

Manufacturing Site: IBSA (b) (4) Switzerland

Method of Sterilization: N/A. This is a non-sterile drug product.

Review Summary: Recommended for Approval

List Submissions being reviewed: 2/26/2016, 6/20/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: N/A

Remarks Section: N/A

S Drug Substance

Not applicable

P.1 Description of the Composition of the Drug Product

- Description of drug product – Non-sterile solution
- Drug product composition –

Ingredient	Content per unit
Levothyroxine sodium	0.013 – 0.200 mg
Glycerol (b) (4) % w/w)	(b) (4)

- Description of container closure system –

A strip of five white, non-transparent, LDPE unit-dose ampoules. Ampoules are supplied by (b) (4)

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbiological quality for this non-sterile product.

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

N/A, container closure integrity is not required for a non-sterile product.

Antimicrobial Effectiveness Testing

N/A, this non-sterile product is not a multiple dose product and therefore it does not contain a preservative.

(b) (4)

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A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable.

(b) (4)

[redacted]

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

- Store the unopened pouch at 25 °C. After opening the outer pouch, the single-dose ampoules must be used within 15 days. [redacted] (b) (4) The unused diluted solution can not be stored.

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Julie Nemecek, Ph.D., 6/30/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
I concur with the primary reviewer's assessment. John W. Metcalfe, Ph.D. 6/30/2016

John Metcalfe

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Julie Nemecek

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Su (Suong) Tran

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