

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206977Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206977

SUPPL #

HFD #

Trade Name: Tirosint-SOL

Generic Name: levothyroxine sodium oral solution

Applicant Name: Institut Biochimique SA (IBSA)

Approval Date: December 16, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

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 mcg under fasting conditions in healthy volunteers. The results showed the following:

- **Levothyroxine sodium oral solution taken with water is bioequivalent to Tirosint capsules according to the baseline corrected levothyroxine C_{max}**

- and AUC0-48h parameters under fasting conditions.
- **Levothyroxine sodium oral solution taken without water is bioequivalent to Tirosint capsules according to the baseline corrected levothyroxine Cmax and AUC0-48h under fasting conditions.**
 - **Levothyroxine sodium oral solution taken with water is bioequivalent to Tirosint capsules according to the baseline uncorrected levothyroxine Cmax and AUC0-48h under fasting conditions.**
 - **Levothyroxine sodium oral solution taken without water is bioequivalent to Tirosint capsules according to the baseline uncorrected levothyroxine Cmax and AUC0-48h under fasting conditions.**

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21342	Levo-T
NDA# 21210	Unithroid
NDA# 21301	Levoxyl

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#
NDA#
NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO

THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would

not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Name of person completing form: Linda V. Galgay
Title: Sr. Regulatory Project Manager
Date: 11/28/16

Name of Division Director signing form: Jean-Marc Guettier, MD
Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA V GALGAY
12/04/2016

MARINA ZEMSKOVA
12/04/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206977	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Tirosint-SOL Established/Proper Name: levothyroxine sodium oral solution Dosage Form: solution		Applicant: Institut Biochimique SA(IBSA) Agent for Applicant (if applicable): Cromsource Inc.
RPM: Linda Galgay		Division: Metabolism and Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: December 15, 2016</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action 12/15/16 User Fee Goal Date is 12/26/16 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 3 New Dosage Form
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date 12/15/16
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included – See PI attached to approval letter
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Patient Package Insert/Instructions for Use/ (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included – See patient labeling attached to approval letter
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included – See labels attached to approval letter
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability letter Review 	5/24/16 5/20/16
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: DMEPA: 9/7/16 OPDP: 12/8/16 DMPP/PLT: 11/8/16 Consult Review: PMHS: 11/10/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: refer to Quality Review 11/10/16 (Drug Product Review/E.Luong/D.Christodoulou 9/29/16)
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	11/28/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	11/28/16
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Completed 12/4/16 CDTL for DD
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC If PeRC review not necessary, explain: _____ 	11/2/16
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Pre-NDA (<i>indicate date of mtg</i>) 	6/20/13
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) M.Zemskova	12/5/16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
• Clinical review (<i>indicate date for each review</i>) J.Sharretts		12/6/16, 5/10/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Financial Disclosure review	J.Sharretts	12/6/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> N/A
❖ Risk Management		
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)		N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)		N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)		<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)		<input checked="" type="checkbox"/> None requested
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input checked="" type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review((<i>indicate date for each review</i>)S.Lau/J.vaidyanathan		11/6/16, 4/19/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		8/8/16

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) P.Espandiar/C.Elmore	11/7/16, 4/13/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	N/A
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	N/A
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>) Executive Summary: S.Tran 11/10/16 Drug Substance: D.Christner/ J.Medwid 10/19/16 Drug Product, Environmental Assessment (DP page 28), and Labeling: E.Luong/D.Christodoulou 9/29/16 Process: E.Kim/N.Chidambaram 10/21/16 Facilities: J.Williams/D.Lech 10/19/16 Biopharmaceutics: P.Duan/H.Mandula 9/29/16 Microbiology: J.Nemecek/J.Metcalf 10/19/16	11/10/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) (see Product Quality Review, Drug Product page 28)	11/10/16
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: N/A <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA V GALGAY
12/21/2016

From: Susan Gamble [mailto:Susan.Gamble@cromsource.com]
Sent: Friday, December 16, 2016 10:25 AM
To: Galgay, Linda
Subject: RE: Approval NDA 206977/Tirosint-SOL

Dear Linda,
Thank you for all your help.

I have forwarded the TIROSINT-SOL Approval Letter to IBSA.

It has been a pleasure working with you.

Regards,

Susan Gamble, PhD, RAC (US) | Senior Director, Regulatory Affairs
Ph + [REDACTED] Skype susangamblecrom

From: Galgay, Linda
Sent: Thursday, December 15, 2016 7:00 PM
To: susan.gamble@cromsource.com
Subject: Re: Approval NDA 206977/Tirosint-SOL
Importance: High



16 1215 EMAIL AP
NDA 206977 Ti...

Dear Susan,

Please find attached a copy of the approval letter that issued today for NDA 206977, for Tirosint-SOL. You will also receive a copy in the mail. Please confirm receipt of this email.

It has been a pleasure to work with you.

Best regards,

Linda

Linda V. Galgay, RN, MSN
Sr. Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-5383
Fax: 301-796-9712
linda.galgay@fda.hhs.gov

**PeRC Meeting Minutes
November 2, 2016**

PeRC Members Attending:

Lynne Yao
John Alexander
Jacqueline Yancy
Meshaun Payne
Hari Cheryl Sachs
Raquel Tapia
Tom Smith
Wiley Chambers
Kevin Krudys
Lily Mulugeta
Freda Cooner
Victor Baum
Daiva Shetty
Skip Nelson
Gil Burkhart
Adrienne Hornatko-Munoz
Barb Buch

Agenda

9:00	NON-RESPONSIVE				
9:20	NON-RESPONSIVE				
9:40	NON-RESPONSIVE				
10:00	NON-RESPONSIVE				
10:10	NON-RESPONSIVE				
10:30	NON-RESPONSIVE				
10:40	NON-RESPONSIVE				
10:55	NDA 206977	TIROSINT-SOL (levothyroxine sodium) Oral Solution (Assessment) with Agreed iPSP	DMEP	Linda Galgay	Hypothyroidism/Pituitary TSH Suppression
11:05	NON-RESPONSIVE				
	NON-RESPONSIVE				

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NON-RESPONSIVE

TIROSINT-SOL (levothyroxine sodium) Oral Solution (Assessment) with Agreed iPSP

- Indication: Hypothyroidism/Pituitary TSH Suppression
- These products trigger PREA for new regimen, new dosage form and new route of administration. The PDUFA goal date is 12/23/2016.
- The division states that no additional pediatric studies are needed at this time because the product is appropriately labeled for use in all relevant pediatric populations.
- The division agreed that there is bioequivalence and that the dosing can be provided for dosage down to birth. The PeRC reviewed the iPSP which was agreed upon and state that it is bioequivalent down to birth and is able to be labeled down to birth.

- *PeRC Recommendations:*
 - The PeRC concurred with the division's assessment.

NON-RESPONSIVE

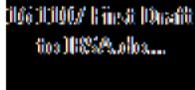
2 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

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/s/

JACQUILINE A YANCY
12/01/2016

From: Galgay, Linda
Sent: Monday, November 07, 2016 12:38 PM
To: susan.gamble@cromsource.com
Subject: Re: First Draft PI/NDA 206977/Tirosint-SOL
Importance: High



Dear Susan,

Please find attached the First Draft of the PI for Tirosint-SOL . This will not be our final version; there will be additional changes and questions for you as we complete our review.

Prior to returning the PI to FDA by COB Wednesday, November 16, 2016:

1. Accept all track changes/edits that you agree with.
2. Address specific comments directed to Applicant. Respond in the comment bubbles if you agree or disagree with our comments.
3. Ensure uniformity of spacing and justification throughout.
4. Verify that the numbers are correct and match throughout. The numbers referenced in Highlights section must match the numbers in Table of Contents and the numbers in Full Prescribing Information.

Do not submit anything to the NDA until we have agreed upon a final label. **Please acknowledge the receipt of this email.**

Please call me should you have questions,

Best regards,

Linda

Linda V. Galgay, RN, MSN
Sr. Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-5383
Fax: 301-796-9712
linda.galgay@fda.hhs.gov

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/s/

LINDA V GALGAY
11/27/2016

MEMORANDUM

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

DATE: 8/8/2016

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 206977

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	inVentiv Health Clinique, Inc.	2500 Rue Einstein, Quebec City, Quebec, Canada

MEMORANDUM

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

DATE: 8/2/2016

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 206977

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
08/08/2016



NDA 206977

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Institut Biochimique SA (IBSA)
c/o Cromsource, Inc.
One Alewife Center, Suite 120
Cambridge, MA 02140

ATTENTION: Susan M. Gamble, PhD, RAC (US)
US Agent, IBSA
Senior Director, Regulatory Affairs, Cromsource Inc.

Dear Dr. Gamble:

Please refer to your New Drug Application (NDA) dated and received February 26, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium 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 and 200 mcg/mL.

We also refer to your correspondence, dated and received March 9, 2016, requesting review of your proposed proprietary name, Tirosint-SOL.

We have completed our review of the proposed proprietary name, Tirosint-SOL and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 9, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,

<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Linda Galgay, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
05/24/2016



NDA 206977

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Cromsource, Inc.
Agent for Institut Biochimique SA (IBSA)
Attention: Susan Gamble, PhD, RAC(US)
Senior Regulatory Director
One Alewife Center, Suite 120
Cambridge, MA 02140

Dear Dr. Gamble:

Please refer to your New Drug Application (NDA) dated and received February 26, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for levothyroxine sodium oral solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 26, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 26, 2016.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information.

1. CLINICAL PHARMACOLOGY

- a. Are the 0.15 mg Tirosint capsules tested in Study 140161-14CDN/T403 approved and marketed in the United States?
- b. The report for Study 140161-14CDN/T403 provided the bioequivalence assessment between levothyroxine sodium oral solution (LSOS) with water and Tirosint capsule for the baseline-corrected levothyroxine pharmacokinetic parameters. Provide the following for Study 140161-14CDN/T403:
 - i. The bioequivalence assessment between LSOS without water and Tirosint capsule for the baseline corrected levothyroxine PK parameters.
 - ii. The bioequivalence assessment for the baseline-uncorrected levothyroxine pharmacokinetic parameters for the following:
 - a) between LSOS with water and Tirosint capsule
 - b) between LSOS without water and Tirosint capsule
 - c) between LSOS without water and LSOS with water

2. PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

a. GENERAL FORMAT of LABELING

Resubmit labeling (in Microsoft Word format) that addresses the following issues by **June 1, 2016**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

- i. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”
- ii. For drug products other than vaccines, the verbatim **bolded** statement must be present: **“To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”**
- iii. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

b. REQUIREMENTS for PREGNANCY and LACTATION LABELING

Your prescribing information (PI) must comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. Therefore, resubmit labeling in PLLR format by July 15, 2016. The submission should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the *draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This drug may be fully labeled for use in all appropriate pediatric populations. We will notify you if we determine that the current pediatric labeling is not adequate. If we determine that the current pediatric labeling is not adequate, you will need to submit a pediatric plan, or request a waiver or deferral for the relevant pediatric age groups.

If you have any questions, call Linda Galgay, Regulatory Project Manager, at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LINDA V GALGAY
05/10/2016

JEAN-MARC P GUETTIER
05/10/2016

Begin forwarded message:

From: "Galgay, Linda" <Linda.Galgay@fda.hhs.gov>
Date: September 29, 2013 11:00:11 AM PDT
To: CLARENCE JONES <cejtwsex@verizon.net>
Subject: Re: IND 115023 LSOS

Hi CJ,

I received the following response from the Biopharmaceutics team:

Your plan to request a biowaiver for not only the lower dosage strengths (below 150 mcg/mL) but also for the 175 and 200 mcg/mL dosage strengths can be granted based on demonstration of compositional proportionality among different strengths and linear PK of the drug substance across the entire range. Please submit this information for the Agency to review.

Best regards,

Linda

Linda V. Galgay, RN, MSN
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-5383
Fax: 301-796-9712
linda.galgay@fda.hhs.gov

From: CLARENCE JONES [<mailto:cejtwsex@verizon.net>]
Sent: Thursday, September 26, 2013 10:39 AM
To: Galgay, Linda
Subject: Re: Re: IND 115023 LSOS

Hi Linda,

The primary reason for posing the Biopharmaceutics question is that IBSA has assumed that (although it wants to gain approval for 175 and 200 mcg LSOS) it should compare 150 mcg LSOS to 150 Tirosint since the the latter is the highest dosage strength approved at this time pending approval of the Tirosint 175 and 200 mcg dosage strengths which presumably will occur once the capsule identification issue is resolved. If IBSA does compare 150 mcg LSOS to 150 Tirosint can they request a biowaiver for not only the lower dosage strengths but also the 175 and 200 mcg LSOS dosage strengths given that there are no issues relating to dissolution of a liquid formulation? This proposal seems to be generally consistent with the Pre-NDA Meeting Minutes - Question 2 below, but IBSA would like to be certain.

Thanks for the further clarification!
CJ

Question 2 Discussion

*In the case of reformulation [REDACTED] ^{(b) (4)} a new bioequivalence (BE) study would be needed and an additional biowaiver would need to be requested. In essence, a new BE study needs to be conducted **possibly** with the highest strength of each formulation followed by a biowaiver request for the lower strengths of that particular formulation.*

From: "Galgay, Linda" <Linda.Galgay@fda.hhs.gov>
To: CLARENCE JONES <cejtwsex@verizon.net>
Sent: Wednesday, September 25, 2013 10:46 AM
Subject: RE: Re: IND 115023 LSOS

Dear CJ,

Regarding IBSA's July 22, 2013, response to our July 3, 2013, meeting minutes, I have the following additional comment.

Biopharmaceutics:

Submit a biowaiver request with supportive information and justification in the NDA for any strength that is not tested in the new BE study. It is expected the BE will be established between the proposed and reference product at the highest strength and a biowaiver will be requested for the lower strengths.

Clinical Pharmacology and Clinical have no additional comments.

Thanks very much,

Linda



NDA 206-977
Levothyroxine Sodium Oral Solution
IBSA Institut Biochimique SA

Reviewer: S.W. Johnny Lau
Team Leader: Jaya Vaidyanathan

Office of Clinical Pharmacology



NDA 206-977

- This is a 505(b)(2) submission for levothyroxine sodium oral solution (LSOS).
- References: Tirosint capsule and Synthroid tablet
- Levothyroxine is a synthetic thyroid hormone, chemically identical to thyroxine (T4).
- No approved oral solution formulation of levothyroxine sodium is available in the US.
- LSOS is not approved in any other country.



NDA 206-977

- Seeks the following indications and use:
 - treat hypothyroidism
 - suppress pituitary thyrotropin-stimulating hormone (TSH)
 - use in patients < 6 years of age*
- Dosing must be individualized.

* Tirosint capsules are contraindicated for patients < 6 years of age.



NDA 206-977

- Proposed 12 strengths of LSOS:
 - 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 µg/mL
- Tirosint oral capsule has 10 approved strengths:
 - 13, 25, 50, 75, 88, 100, 112, 125, 137, and 150 µg
- Synthroid tablet has 12 approved strengths:
 - 25, 50, 75, 88, 100, 112, 125, 137, 15, 175, 200, and 300 µg



NDA 206-977

- Requested biowaiver for 11 strengths of LSOS except the 150 µg/mL strength (BE assessed in Study 403)
- Tirosint 150 µg capsule is the RLD for LSOS 13 – 150 µg/mL strengths.
- Synthroid 300 µg tablet is the RLD for LSOS 175 and 200 µg/mL strengths.



NDA 206-977

- Only 3 Clinical Pharmacology studies to support this NDA:
 - 130284/13CDN/T406 (Study 406, failed study)
 - 140143/14CDN/T405 (Study 405, pilot BE study)
 - 140161/14CDN/T403 (Study 403, pivotal BE study)



Study 403

- Pivotal BE Study:
 - 4 mL of 150 $\mu\text{g}/\text{mL}$ levothyroxine oral solution with 240 mL water
 - 4 mL of 150 $\mu\text{g}/\text{mL}$ levothyroxine oral solution without water
 - 4 of 150 μg Tirosint oral capsules with 240 mL water
- The 150 μg Tirosint oral capsule is the reference listed drug (RLD) in the US.
- All treatments occurred under fasting.



Study 403

Table 2.5-4 Ratios and Confidence Intervals for Baseline-Corrected Levothyroxine Pharmacokinetic Results in Study 140161 – 14CDN/T403

Parameter	Treatment Comparisons	Ratio ^a	90% Geometric C.I. ^b		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC ₀₋₄₈	LSOS with water – Tirosint	98.47%	94.97%	102.11%	8.99%	22.42%
	LSOS without water – LSOS with water	102.72%	98.98%	106.60%		
C _{max}	LSOS with water – Tirosint	95.33%	91.97%	98.82%	8.91%	21.36%
	LSOS without water – LSOS with water	99.28%	95.70%	102.99%		

Calculated using least-squares means according to the formula: $e^{(\text{DIFFERENCE})} \times 100$.
90% Geometric Confidence Interval using ln-transformed data.



OSI

- Need to request inspection of the pivotal BE Study 140161-14CDN/T403 for the:
 - Clinical Site
 - Bioanalytical Site



Filing Status for Levothyroxine Sodium Oral Solution

- Clinical Pharmacology recommends NDA 206-977 to be **fileable** because:
 - Clinically-tested formulation is the same as the to-be-marketed formulation.
 - Provided BE data to link the 150 µg/mL LSOS and the 150 µg Tirosint capsule (RLD).
 - Provided biowaiver request for a dosage-form proportionality study for the lower and higher strengths of LSOS.
 - OPQ Biopharmaceutics will review justification for the link between 175 + 200 µg/mL LSOS and 300 µg Synthroid tablet (RLD).
 - Provided bioanalytical and validation reports as well as electronic datasets for Studies 403 and 405.
 - Annotated proposed label of LSOS for review.



Information Request

- Is the Tirosint capsules tested in Study 403 approved and marketed in the United States?
- Study 403's report provided the BE assessment between LSOS with water and Tirosint capsule for the baseline-corrected levothyroxine PK parameters. The sponsor needs to provide the following for Study 403:
 - The BE assessment between LSOS without water and Tirosint capsule for baseline-corrected levothyroxine PK parameters.
 - The BE assessment for baseline-uncorrected levothyroxine PK parameters for the following:
 - between LSOS with water and Tirosint capsule
 - between LSOS without water and Tirosint capsule
 - between LSOS without water and LSOS with water

Review Focus

- Is the LSOS (150 $\mu\text{g}/\text{mL}$) taken with water bioequivalent to the 150 μg Tirosint capsule under fasting?
- Is the LSOS (150 $\mu\text{g}/\text{mL}$) taken without water bioequivalent to the 150 μg Tirosint capsule under fasting?



U.S. Food and Drug Administration
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Backup Slides



Study 405

Table 2.7.1-17 Ratios, 90% Geometric Confidence Intervals for AUC₀₋₄₈ and C_{max} for Baseline-Corrected Levothyroxine for Study 140143

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC ₀₋₄₈	Test(A)-Reference 1(B)	101.37%	91.45%	112.36%	11.50%	14.61%
	Reference 2(C)-Reference 1(B)	112.00%	101.04%	124.15%		
C _{max}	Test(A)-Reference 1(B)	92.45%	84.31%	101.39%	10.30%	12.31%
	Reference 2(C)-Reference 1(B)	106.37%	97.00%	116.65%		

¹ Calculated using least-squares means according to the formula: $e^{(\text{Difference})} \times 100$.

² 90% Geometric Confidence Interval using ln-transformed data.



Study 406

Table II: Baseline Corrected Levothyroxine - Ratios, 90% Geometric Confidence Intervals, Intra- and Inter-Subject CVs

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC ₀₋₄₈	Test 1 (A) - Reference (C)	70.48%	55.40%	89.65%	60.87%	27.19%
	Test 2 (B) - Test 1 (A)	100.93%	79.81%	127.63%		
C _{max}	Test 1 (A) - Reference (C)	76.37%	66.44%	87.79%	33.39%	24.02%
	Test 2 (B) - Test 1 (A)	94.91%	82.85%	108.73%		

¹ Calculated using least-squares means according to the formula: $e^{(\text{DIFFERENCE})} \times 100$.

² 90% Geometric Confidence Interval using ln-transformed data.



BE Assessment Practice

OGD	OCP
Analyte = levothyroxine	Analyte = levothyroxine
Baseline-corrected BE	Baseline unadjusted BE
Separate fasting BE study and Separate fed BE study, if appropriate	Fasting BE study
Fully replicated crossover study design	2-treatment-sequence-crossover study design
Product Specific Guidance (Dec 2014): <ul style="list-style-type: none"> Levothyroxine sodium 	Guidance for Industry (Dec 2000): <ul style="list-style-type: none"> Levothyroxine Na Tab PK BA Dissolution

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/s/

SZE W LAU
04/18/2016

JAYABHARATHI VAIDYANATHAN
04/19/2016



NDA 206977

NDA ACKNOWLEDGMENT

Cromsource, Inc.
Agent for Institut Biochimique SA (IBSA)
Attention: Susan Gamble, PhD, RAC(US)
Senior Regulatory Director
One Alewife Center, Suite 120
Cambridge, MA 02140

Dear Dr. Gamble:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

Date of Application: February 26, 2016

Date of Receipt: February 26, 2016

Our Reference Number: NDA 206977

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **April 26, 2016**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Linda V. Galgay, RN, MSN
Sr. Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA V GALGAY
04/04/2016



IND 115023

MEETING MINUTES

Institut Biochimique SA (IBSA)
Attention: Clarence E. Jones, Ph.D.
IBSA U.S. Agent
4249 Via Encanto
Thousand Oaks, CA 91320

Dear Dr. Jones:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for levothyroxine sodium oral solution.

We also refer to the meeting between representatives of IBSA and the FDA on June 20, 2013. The purpose of the meeting was to discuss the development program to support the submission of a 505(b)(2) New Drug Application (NDA) for levothyroxine sodium oral solution in patients requiring levothyroxine replacement therapy or pituitary TSH suppression.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Linda Galgay, Regulatory Project Manager, at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

On June 27, 2012, the Division provided written responses to a March 21, 2012, pre-IND meeting request. IBSA submitted IND 115033 on September 24, 2012, and an advice/information request letter issued on November 7, 2012.

The primary purpose of this meeting was to receive further guidance as to whether there were outstanding issues related to the product, or to the developmental plan conducted by the sponsor that needed to be addressed before proceeding with a NDA submission for LSOS in patients requiring levothyroxine replacement therapy or pituitary TSH suppression.

In a June 13, 2013, email to the project manager IBSA requested that the meeting discussion focus on the following prioritized items:

- Question number 4
- PREA requirement and pediatric labeling (section 4.0)
- Packaging configuration and labeling (section 2.4 of the letter)

On June 25, 2013, IBSA submitted additional information for the meeting to the IND.

2. DISCUSSION

Questions are in regular text. Preliminary responses are in **bolded** text. Discussion is in *italicized* text. Additional comments are in **bolded, italicized** text.

2.1. BIOPHARMACEUTICS

IBSA Question 1: Is the BA/BE data on 150 mcg, the recommended dose as per the 06/27/2012 FDA Letter, sufficient to support a 505(b)(2) NDA submission for the full range of proposed dosage strengths, including 175 and 200 µg/mL?

FDA Response to Question 1:

Yes, your plan to provide BA/BE data on the 150 mcg/mL strength is acceptable. Include the biowaiver request for all other strengths with a justification as part of the NDA submission.

Discussion regarding Question 1:

There was no discussion regarding Question 1.

IBSA Question 2: On the basis of the demonstrated bioequivalence between the oral solution taken with or without water, IBSA would like to state on the label that

“(b) (4)”. Is this acceptable for the Agency?

FDA Response to Question 2:

In general, you may describe the study condition(s) in labeling if the resulting data are acceptable. However, we can not agree on specific labeling at this time because acceptability of the data is a review issue.

Discussion regarding Question 2:

In the case of reformulation [REDACTED] (b) (4) a new bioequivalence (BE) study would be needed and an additional biowaiver would need to be requested. In essence, a new BE study needs to be conducted possibly with the highest strength of each formulation followed by a biowaiver request for the lower strengths of that particular formulation.

A new study evaluating the effect of water on the oral solution may also be necessary in the case of reformulation of the product.

2.2. CLINICAL

IBSA Question 3: For pediatric population below 6 year of age, IBSA will rely on the standard labeling currently used for all approved levothyroxine sodium products with regards to usage, dosing procedure and therapy monitoring. Is this acceptable for the Agency?

FDA Response to Question 3:

There is no uniform “standard labeling” for all approved levothyroxine products. Appropriate wording should be proposed at the time of NDA submission and will be a review/labeling negotiation issue at that time.

Discussion regarding Question 3:

There was no discussion regarding Question 3.

IBSA Question 4: Does the Agency consider the proposed exception to standard pediatric labeling adequate [REDACTED] (b) (4)? [See Product Insert, Dosage and Administration (2.3) section]

FDA Response to Question 4:

[REDACTED] (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
07/03/2013



IND 115023

MEETING MINUTES

Institut Biochimique SA (IBSA)
Attention: Clarence E. Jones, Ph.D.
IBSA U.S. Agent
4249 Via Encanto
Thousand Oaks, CA 91320

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Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, June 20, 2013, 2:00 – 3:00 pm ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: 115023
Product Name: levothyroxine sodium oral solution (LSOS)
Indication: levothyroxine replacement therapy or pituitary TSH suppression
Sponsor/U.S. Agent Name: Institut Biochimique SA (IBSA) (Switzerland)/
Clarence E. Jones, Ph.D.

Meeting Chair: Mary Parks
Meeting Recorder: Linda Galgay

FDA ATTENDEES

Office of Drug Evaluation II, Division of Metabolism and Endocrinology Products

Mary Parks, MD	Director
Dragos Roman, MD	Clinical Team Leader
Naomi Lowy, MD	Clinical Reviewer
Parvaneh Espandari, PhD	Pharmacology/Toxicology Reviewer
Linda Galgay, RN, MSN	Regulatory Project Manager

Office of New Drug Quality Assessment III

Eric Duffy, PhD	Director
Tapash Ghosh, PhD	Biopharmaceutics Team Leader

Office of Translational Sciences, Office of Clinical Pharmacology

Immo Zadezensky, PhD	Team Leader, Division of Clinical Pharmacology 2
Sang Chung, PhD	Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis

Carol Holquist, RPh	Director
Yelena Maslov, PharmD	Safety Team Leader
Agustin Reasol, PharmD	Safety Evaluator

INSTITUT BIOCHIMIQUE SA (IBSA) ATTENDEES

Giuseppe Mautone	R&D Director
Claudia Scarsi	Clinical Research Manager
Alberto Bernareggi	Director, IBSA Pharmaceutical Research and Development
Elena Papis	Regulatory Affairs Officer
Clarence Jones	U.S. Agent

1.0 BACKGROUND

Institut Biochimique SA (IBSA) is developing levothyroxine sodium oral solution (LSOS) for 12 dosage strengths (13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg/mL). Levothyroxine sodium is L-thyroxine (T4) and is indicated for:

- **Hypothyroidism** - As replacement (b) (4) therapy in congenital or acquired hypothyroidism (b) (4)
- **Pituitary Thyrotropin-Stimulating Hormone (TSH) Suppression** - As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer

According to IBSA, the principal advantages of an oral solution, as compared to solid dosage forms, are the ease of manufacture that lead to the virtual absence of within batch (inter-unit) variability, and the ease of administration, which makes it particularly suitable for patients with impaired swallowing and small children (less than 6 years of age) who are generally not able to swallow intact tablets or capsules.

The LSOS NDA proposes to rely on FDA findings of safety and effectiveness for the Listed Drug Tirosint (Levothyroxine sodium capsules) (NDA 21924, sponsor IBSA), as well as Synthroid, the Listed Drug for Tirosint capsules in its approved NDA. The proposed indications are identical to those of both Listed Drugs: hypothyroidism and pituitary TSH suppression.

The following two *in vivo* biopharmaceutic studies were performed with LSOS:

Study #	Route	Study Design	Subject # Enrolled/ Evaluated	Conclusion
120118	Oral	Randomized, open -label, 2-way cross-over comparing a 600 mcg total dose of LSOS and Tirosint capsules, each provided in 150 mcg dosage strengths.	32/30	A 600 mcg total dose of LSOS and Tirosint capsules were bioequivalent.
120328	Oral	Randomized, open-label, 3-way cross-over comparing 600 mcg total dose of LSOS in fasting and fed subjects (LSOS diluted in water), and fasting subjects for whom LSOS was dispensed directly into the oral cavity. 100 mcg ampules were tested.	14/14	A 600 mcg total dose of LSOS was bioequivalent in fasting subjects when administered either following dilution in water or introduction directly into the oral cavity, but not bioequivalent in fasting and fed subjects.

On June 27, 2012, the Division provided written responses to a March 21, 2012, pre-IND meeting request. IBSA submitted IND 115033 on September 24, 2012, and an advice/information request letter issued on November 7, 2012.

The primary purpose of this meeting was to receive further guidance as to whether there were outstanding issues related to the product, or to the developmental plan conducted by the sponsor that needed to be addressed before proceeding with a NDA submission for LSOS in patients requiring levothyroxine replacement therapy or pituitary TSH suppression.

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IBSA Question 1: Is the BA/BE data on 150 mcg, the recommended dose as per the 06/27/2012 FDA Letter, sufficient to support a 505(b)(2) NDA submission for the full range of proposed dosage strengths, including 175 and 200 µg/mL?

FDA Response to Question 1:

Yes, your plan to provide BA/BE data on the 150 mcg/mL strength is acceptable. Include the biowaiver request for all other strengths with a justification as part of the NDA submission.

Discussion regarding Question 1:

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IBSA Question 2: On the basis of the demonstrated bioequivalence between the oral solution taken with or without water, IBSA would like to state on the label that

“
[REDACTED] (b) (4)
[REDACTED] . Is this acceptable for the Agency?

FDA Response to Question 2:

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Discussion regarding Question 2:

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FDA Response to Question 3:

There is no uniform “standard labeling” for all approved levothyroxine products. Appropriate wording should be proposed at the time of NDA submission and will be a review/labeling negotiation issue at that time.

Discussion regarding Question 3:

There was no discussion regarding Question 3.

IBSA Question 4: Does the Agency consider the proposed exception to standard pediatric labeling adequate [REDACTED] ^{(b) (4)}? [See Product Insert, Dosage and Administration (2.3) section]

FDA Response to Question 4:

[REDACTED] ^{(b) (4)}

Given these concerns, and considering that you have developed this formulation, in part, for ease of administration in small children, [REDACTED] (b) (4)

If you do choose to go forward with the current formulation and your proposed product usage limitation, you would need to request a waiver for the appropriate age group (refer to Section 4).

Discussion regarding Question 4:

Prior to the meeting, you provided the Division with an updated proposal [REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

2.3. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

IBSA Question 5: Extractables from the primary closure system were evaluated using the solvents [REDACTED] (b) (4), under forced extraction conditions. Due to the formulation composition [REDACTED] (b) (4).

[REDACTED] Does the Agency agree that the solvents used are sufficient to assess the extractable profile of the primary closure system for LSOS, and that the results of the extractable study allow for the proper planning of a leachable study?

FDA Response to Question 5:

In addition to the proposed solvents, we recommend that you also use the placebo vehicle (i.e., [REDACTED] (b) (4) % glycerol) in your extraction study.

Discussion regarding Question 5:

There was no discussion regarding Question 5.

IBSA Question 6: Are there any outstanding issues relating to product manufacture or control that need to be addressed before proceeding with a 505(b)(2) NDA submission for 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 µg/mL LSOS?

FDA Response to Question 6:

We remind you to include in the NDA the following:

- A summary of differences between your product and the referenced product relied upon, including differences in formulation and primary container closure system.
- Information on the potential impurities arising from the drug interaction with excipients and/or container closure system, and from potential degradation pathways.
- Safety information to qualify any proposed impurity/degradants limit that exceeds the applicable ICH qualification threshold for the maximum daily dose of your product (we refer you to ICH Q3B(R2) Impurities in New Drug Products at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf>).
- A complete list of all testing and manufacturing facilities used for the commercial drug substances and drug product in Form 356h of the NDA, with contact information and a statement that all facilities will be ready for the GMP inspection at the time of the NDA submission.

Discussion regarding Question 6:

There was no discussion regarding Question 6.

POST-MEETING NOTE:



2.4 DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)

In your April 29, 2013, submission, you stated that, “Levothyroxine Sodium Oral Solution (LSOS) is supplied in white, non-transparent, low-density polyethylene unit-dose ampules filled to a nominal volume of ^{(b) (4)}1 mL. A strip of five ampules is packaged in ^{(b) (4)} envelope. The final packaging configuration will consist of a box with six envelopes to assure a thirty days supply of drug product, the typical prescription for levothyroxine replacement patients in the U.S.”

Please ensure that the packaging configuration of your choice (i.e., LDPE ampule) is not similar to the currently marketed products in similar packaging configurations (i.e., respiratory inhalation, ophthalmic solutions, and injectable products), because such similarity can increase the risk of confusion regarding the correct route of administration (i.e., oral vs. inhalation, ophthalmic, or injection). We have postmarketing reports that have shown that wrong route of administration errors have occurred due to misleading packaging (e.g., previously a lotion was packaged in a container resembling ophthalmic solution).

Additionally, your proposed package insert states that, “The dosage strength is (b) (4) identified (b) (4) on the box (b) (4), and is associated with a distinct color. Each ampule bears a label with the dosage strength and the product name (TIROSINT-SOL).”

Although you are proposing to use different colors to differentiate box and envelopes of each strength of the product, please ensure sufficient differentiation among the actual ampules of the product. We have post-marketing error reports demonstrating confusion has occurred among LDPE ampules due to small differences in shape, color, and the fact that the drug names are embossed into the plastic in transparent, raised letters, making it difficult to read

***(<http://www.ismp.org/newsletters/acutecare/articles/20020515.asp>;
[http://patientsafetyauthority.org/ADVISORIES/AdvisoryLibrary/2005/jun2\(2\)/Pages/15.aspx](http://patientsafetyauthority.org/ADVISORIES/AdvisoryLibrary/2005/jun2(2)/Pages/15.aspx))***

Please bring samples of the proposed ampules to the Pre-NDA meeting.

Discussion regarding DMEPA’S additional comments (2.4):

You provided samples of the LDPE ampules represented by white plastic ampules with (b) (4) labels with black writing of the product’s name and strength. Five of LDPE vials were placed in one foil pouch. Because of your proposed container closure system configuration and the choice of a (b) (4) black label on the LDPE ampule, we voiced concerns that the proposed packaging configuration may result in medication errors due to the similarity of the LDPE vials to each other within your proposed levothyroxine line as well as to other LDPE ampules for inhalation and ophthalmic products. We pointed out that levothyroxine products in the US contain color coordinated labeling according to the strength. Your proposed product should comply with the same color scheme because that is the color scheme to which healthcare providers and patients are accustomed. If you decide to employ the black (b) (4) labels, provide a Human Factors Study demonstrating that consumers are able to choose the correct strength of the product. We also stated that having five LDPE ampules in one foil pouch is not acceptable because the ampules will be taken out of the foil pouch and may be confused with other levothyroxine strengths from their own line or other LDPE ampules containing inhalation or ophthalmic products. This scenario is especially possible in hospital settings.

(b) (4)

3.0 **505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Discussion regarding the 505(b)(2) REGULATORY PATHWAY (3.0):

There was no discussion regarding the 505(b)(2) REGULATORY PATHWAY (3.0).

4.0 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities.

For additional guidance on submission of the PSP, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

Discussion regarding PREA REQUIREMENTS (4.0):

There was no discussion regarding PREA REQUIREMENTS (4.0).

5.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

Discussion regarding PRESCRIBING INFORMATION (5.0):

There was no discussion regarding PRESCRIBING INFORMATION (5.0).

6.0 STANDARD LANGUAGE REGARDING U.S. UNITS

All laboratory data in final individual study reports, integrated summaries, and datasets, including those data presented in the form of tables and graphs, supporting an application must be in U.S. (conventional) units.

Discussion regarding STANDARD LANGUAGE REGARDING U.S. UNITS (6.0):

There was no discussion regarding STANDARD LANGUAGE REGARDING U.S. UNITS (6.0).

7.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Discussion regarding MANUFACTURING FACILITIES (7.0):

There was no discussion regarding MANUFACTURING FACILITIES (7.0).

8.0 DATA SUBMISSION

We prefer that sponsors submit datasets based on the Study Data Specifications version published at the time of submission (currently 2.0). However, in general, we accept datasets which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance, based on the timing of protocol design, protocol initiation, and data collection.

We expect sponsors to evaluate the risk involved converting study data collected to standardized data, if applicable. We prefer that sponsors submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario: decision rationale for not converting or decision rationale for converting. We expect that the sponsor's evaluation and rationale includes study data scientifically relevant to the application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The [PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017](#) guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. You should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. You should use the CDISC Technical Road Map to design end-to-end harmonized data standardization, including the [CDASH](#) standard for design and implementation of data collection instruments.

Our methodology and submission structure supports research study design, as indicated in the [Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications](#) and the [Study Data Specifications](#). Our methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits.

You should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See [SEND](#), [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)). Study analyses datasets should be traceable to the tabulations datasets.

In addition, please reference the [CDER Common Data Standards Issues Document](#) for further information on data standardization in submissions.

Discussion regarding DATA SUBMISSION (8.0):

There was no discussion regarding DATA SUBMISSION (8.0).

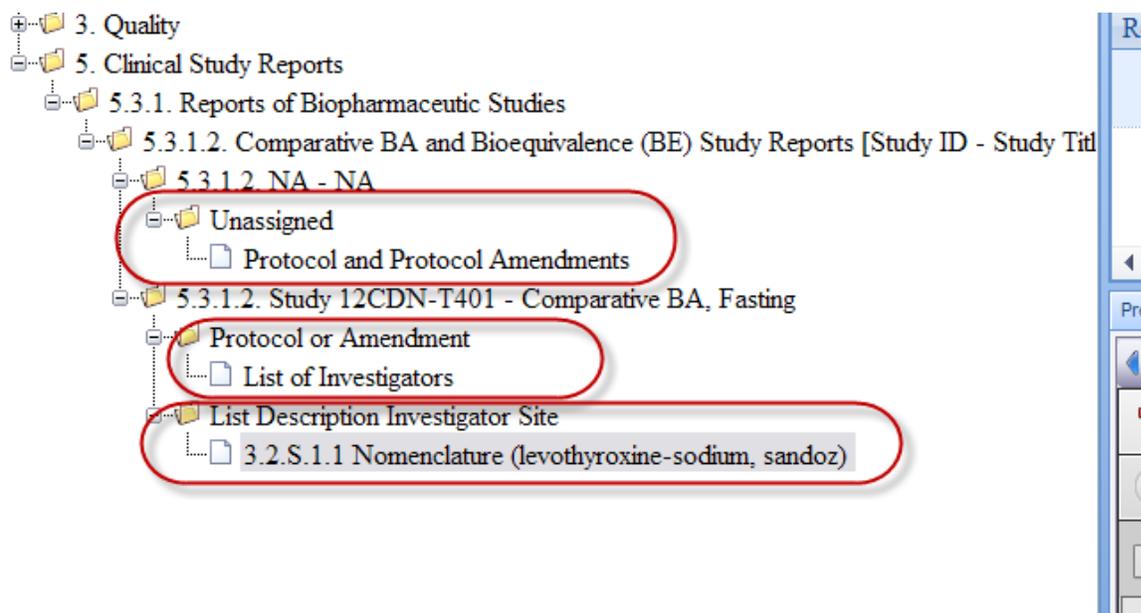
9.0 eCTD STRUCTURE

As soon as possible and prior to submitting the NDA, provide an eCTD sample to esub@fda.hhs.gov. Refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

- Provide a technical point of contact in your cover letter at all times.
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 5 with the exception of 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be correctly tagged and placed under the study's STF including case report forms (crfs). Case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form" and reside with the study's information.
- In sequence 0002 of IND 115023, most of the file tags were incorrectly placed (see snapshot below) In module 5, each study should have its own folder and stf that contains the components for that study. The stf is the study's table of contents and ties all the documents together as well as helps our reviewers see them in a standard display.

You should just have one STF per study and it should have links to all of that study's components and the stf should be placed inside the study's folder (not outside).

- Study Tagging Files (STF) were used incorrectly or not provided, which resulted in the data appearing under an "unassigned" heading element instead of appearing under the appropriate study's file tag (see the screen shot on page 10).
- M3 documents should not reside in m5. Please ensure that documents are placed correctly in their assigned eCTD structure.



Pre-meeting response to eCTD STRUCTURE (9.0) in Preliminary Comments (June 14, 2013, email from Clarence Jones, U.S. Agent, to the project manager):

“...I spoke with the person who prepares our eCTD submissions (80 thus far over 6 products and several thousand since 1994 when she first began), and she immediately knew what the problem was based on the screen-shot on page 11. So her comments are more readily understandable, please note that eCTDs are normally constructed using a Publishing Tool which is then validated with a Validate Tool, and then prior to submission to FDA is vetted using a Viewing Tool. There are numerous Publishing, Validate and Viewing Tools, but unfortunately for eCTD sponsors, everyone must use GlobalSubmit Review for the final step in the process (document vetting/viewing), since this is the software program that FDA uses and there is no requirement that GlobalSubmit's viewing tool be compatible with any of the other Publishing and Validate Tools.

The only time IBSA experienced the issue detailed under 9.0 of the Meeting Preliminary Comments is following its first ESG submission in May, 2009 when the submission constructed with CoreDossier successfully passed GlobalSubmit validation (both at the sponsor and FDA), but it did not display properly in the GlobalSubmit viewing software (although it did in another commercially available viewing software utilized by IBSA). IBSA subsequently started viewing all submissions in GlobalSubmit Review in an effort to ensure that this sort of situation did not re-occur. The older version of GlobalSubmit used at the time of the Tirosint Oral Solution IND submission (GlobalSubmit v4) displayed the Module 5 documents under meaningful headings (e.g., the protocol displayed under the heading “5.3.1.2 Study 12CDN-T401 – Comparative BA, Fasting”), while the newer version of GlobalSubmit (v6, implemented at 7 months after Sequence 0002 submitted) now displays the same information under the “Unassigned” folder. Please note that GlobalSubmit v5 was only used by FDA for a few months and was then returned to the vendor, presumably because of problems associated with its usage.

She also said she spoke with the FDA Office of Business Informatics (OBI), and they confirmed that they're now using the newer version of GlobalSubmit. They weren't aware, however, of the differences in display between the two different versions of GlobalSubmit..."

For the Tirosint Oral Solution NDA, IBSA will provide a sample eCTD prior to the NDA. In addition, IBSA will implement the following changes in an effort to ensure that the issue does not re-occur. First, IBSA will be utilizing a different publishing software (this software will be utilized to generate both the sample eCTD and NDA). Second, IBSA will institute a manual verification of both the index.xml and study tagging files (STFs) whenever files are included in Modules 4 or 5 for which STFs are required. IBSA will implement this manual verification step because IBSA no longer feels that GlobalSubmit software can be trusted to accurately assess whether submissions are compliant.

Discussion regarding eCTD STRUCTURE (9.0):

There was no discussion regarding eCTD STRUCTURE (9.0).

10.0 CROSS-APPLICATION HYPER LINKING

We prefer that you make use of cross-application hyper linking to directly link files from one NDA to another. Please contact CDER's Electronic Submission Support Team at ESUB@fda.hhs.gov.

Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module 1.4.4 (cross reference to other applications), or use cross application links.

To use the first option (placing a cross reference document in m1.4.4), a PDF document would be placed in m1.4.4 (cross reference to other applications) with a description of what is being cross referenced, and where those original documents reside. Hyperlinks to those documents are optional, but could be of help to reviewers, if provided.

To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server; the applications need to include the appropriate prefix in the href links (e.g., nda). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the cross reference and application number (e.g., Cross Ref to nda123456). The cross reference information in the leaf titles allows the reviewer to know that the document resides in another application and what application is being referenced.

Prior to using cross application linking in an application, submit an "**eCTD cross application links**" sample to ensure you are able to successfully use cross application links.

To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov .

Please refer to the Sample Process web page which is located at
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

Discussion regarding CROSS-APPLICATION HYPER LINKING (10.0):

There was no discussion regarding CROSS-APPLICATION HYPER LINKING (10.0).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
07/03/2013