CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206977Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 8, 2016

To: Linda Galgay, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Meena Ramachandra, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 206977
OPDP labeling comments for TIROSINT®-SOL (levothyroxine sodium) oral solution

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On April 16, 2016, OPDP received a consult request from DMEP to review proposed draft labeling, including draft Prescribing Information (PI) and carton and container labeling for TIROSINT®-SOL (levothyroxine sodium) oral solution (TIROSINT-SOL).

OPDP's review of the proposed substantially complete version of the draft labeling is based on the version e-mailed by Linda Galgay on December 4, 2016 titled "16 1202 PI CLEAN FDA to IBSA Begins Round 3.doc." OPDP's comments are provided in the attached version of the substantially complete labeling.

OPDP's review of the proposed carton and container labeling is based on the version e-mailed by Linda Galgay on December 5, 2016. OPDP does not have any comments on the attached carton and container labeling.

A combined OPDP and Division of Medical Policy Programs (DMPP) patient labeling review was conducted and comments on the Patient Package Insert (PPI) and Instructions For Use (IFU) were provided under separate cover on November 8, 2016.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Meena Ramachandra at 240-402-1348 or Meena.Ramachandra@fda.hhs.gov.

40 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MEENA RAMACHANDRA
12/08/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 206977	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Tirosint-SOL Established/Proper Name: levothyroxine sodium oral solution Dosage Form: oral solution Strengths: 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175 and 200 mcg		
Applicant: Institut Biochimique SA (IBSA) (Switzerland)		
Date of Receipt: 2/26/16		
PDUFA Goal Date: 12/26/16	Action Goal Date (if different): 12/16/16	
RPM: Linda Galgay		
Proposed Indications: **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		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 021402 – Synthroid tablets (AbbVie Inc.)	Previous finding of efficacy in a pediatric population (< 6 years) and of efficacy of 175 and 200 mcg doses for the indications of hypothyroidism and pituitary TSH suppression
NDA 021402 – Synthroid tablets (AbbVie Inc.)	Previous finding of safety in a pediatric population (<6 years) and of safety of 175 and 200 mcg doses

*Note: Tirosint NDA 021924 relied on Synthroid NDA 021402 for clinical pharmacology, efficacy and safety information.

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

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. Study 140161's results showed the following:

- Levothyroxine sodium oral solution taken with water is bioequivalent to Tirosint capsules according to the baseline corrected levothyroxine Cmax 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.

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Synthroid (levothyroxine sodium) tablets	021402	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: Synthroid

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form, from capsule/tablet to solution.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative: Levo-T tablets, Levoxyl tablets, Synthroid tablets, Tirosint capsules, and Unithroid tablets

Discontinued alternatives: Levolet tablets, Novothyrox tablets, Thyro-Tabs (Levothroid) tablets

There are approved levothyroxine sodium generic oral tablets listed in the Orange Book.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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
11/28/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206977	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: TIROSINT-SOL Established: levothyroxine sodium oral solution Dosage Form: solution Strengths: 13 mcg/mL, 25 mcg/mL, 50 mcg/mL, 75 mcg/mL, 88 mcg/mL, 100 mcg/mL, 112 mcg/mL, 125 mcg/mL, 137 mcg/mL, 150 mcg/mL, 175 mcg/mL, 200 mcg/mL		
Applicant: Institut Biochimique SA(IBSA)(Switzerland) Agent for Applicant: Cromsource Inc.		
Date of Application: Feb. 26, 2016 Date of Receipt: Feb. 26, 2016 Date clock started after UN: N/A		
PDUFA Goal Date: Dec. 26, 2016	Action Goal Date (if different): Dec. 16, 2016	
Filing Date: April 26, 2016	Date of Filing Meeting: April 11, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication: Hypothyroidism/TSH Suppression		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number: 115023	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☒	☐		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications

Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.*
Forms *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/uc

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	No additional pediatric studies are needed at this time because this product is appropriately labeled for use in all relevant pediatric populations.
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**

m027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☐ ☐	☒ ☒	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☒	☐	
All labeling (PI, PPI, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☒	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	PI, PPI to DMPP 10/14/16
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☒	☐		Pre-NDA 7/3/13
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 11, 2016

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Linda Galgay	Y
	CPMS:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Marina Zemskova, MD		Y
Division Director/	Jean-Marc Guettier, MD		Y
Office Director/Deputy	Curt Rosebraugh, MD/Mary Parks, MD		N/N
Clinical	Reviewer:	John Sharretts, MD	Y
	TL:	Marina Zemskova, MD	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	S.W. Johnny Lau, PhD	Y
	TL:	Jaya Vaidyanathan, PhD	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Parvaneh Espandiari, PhD	Y
	TL:	Calvin (Lee) Elmore, PhD	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Su Tran, PhD	Y
	RBPM:	Anika Lalmansingh, PhD	Y
• Drug Substance	Reviewer:	Jeff Medwid, PhD	N
• Drug Product	Reviewer:	Elise Luong, PhD	N
• Process	Reviewer:	Erin Kim, PhD	N
• Microbiology	Reviewer:	Julie Nemecek, PhD	N
• Facility	Reviewer:	Donald Lech, PhD	N
• Biopharmaceutics	Reviewer:	Peng (Vincent) Duan, PhD Haritha Mandula, PhD/TL	N N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: PPI, IFU)	Reviewer:	Sharon Williams	N
	TL:	Shawna Hutchins	N
OMP/OPDP (PI, PPI, carton and immediate container labels)	Reviewer:	Meena Ramachandra	N
	TL:	Ankur Kalola	N
OSE/DMEPA (proprietary name, PI, PPI, carton/container labels)	Reviewer:	Leeza Rahimi	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	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.

• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: no clinical studies	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jean-Marc Guettier, DMEP Division Director **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 11/2/16	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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
11/28/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: November 4, 2016 **Date consulted** October 10, 2016

From: Jacqueline Spaulding MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: John Sharretts MD, Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Drug: Tirosint-SOL (levothyroxine sodium oral solution)

NDA: 206977

Applicant: Institut Biochimique SA (IBSA)

Subject: Pregnancy and Lactation Labeling

Indication: Tirosint-SOL 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.

Materials Reviewed:

- DPMH consult request for Tirosint-Sol (levothyroxine sodium oral solution) dated October 10, 2016 DARRTS Reference ID 3997060
- Sponsor's submitted background package for NDA 206977, Tirosint-SOL

Consult Question: "Review/Provide verbiage in PI to comply with the PLLR"

INTRODUCTION

On October 10, 2016, the Division of Metabolism and Endocrinology Products (DMEP) consulted DPMH to review and provide input for appropriate format and content of the pregnancy and lactation sections of Tirosint-SOL labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

On February 26, 2016, Institut Biochimique SA (IBSA) submitted a 505(b)(2) NDA for Tirosint-SOL (levothyroxine sodium oral solution) for the following indications:

- Hypothyroidism: as a replacement (b) (4) therapy in congenital or acquired hypothyroidism (b) (4) Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism.
- Pituitary Thyrotropin Stimulating Hormone (TSH) Suppression: as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

For this 505(b)(2) application, IBSA is relying on the Agency's findings of safety and efficacy for the reference listed drug (RLD), Tirosint® (levothyroxine sodium) capsules (NDA 021924). In support of this NDA, IBSA is relying on one pivotal comparative bioavailability study (Study 140161 – 14CDN/T403) to establish the bioequivalence of the new oral solution formulation to Tirosint 150 µg capsule, thus providing a scientific rationale for levothyroxine sodium oral solution (LSOS) reliance on the clinical safety and efficacy data available for the listed drug, Tirosint capsules.

BACKGROUND

Hypothyroidism and Pregnancy

Primary hypothyroidism is the most common endocrine disease, and the prevalence of hypothyroidism in the general population ranges from 3.8%–4.6%. [1] In Western countries, the most common cause of primary hypothyroidism is autoimmune thyroiditis (Hashimoto thyroiditis). In other parts of the world, iodine deficiency still remains an important factor. Other common causes of hypothyroidism include: thyroidectomy, radioiodine therapy, and drugs, such as amiodarone, lithium, thionamide, iodine, interferon, sunitinib, rifampicin, and thalidomide. The common clinical features associated with hypothyroidism include: tiredness, weight gain, dry skin, cold intolerance, constipation, muscle weakness, puffiness around the eyes, hoarse voice, and poor memory.

[1] Chakera, AJ., Simon, SH; Bijay, Vijay. (2011) Treatment for Primary Hypothyroidism: Current Approaches and Future Approaches and Future Possibilities. *Drug Design, Development and Therapy,*

The incidence of hypothyroidism during pregnancy is estimated to be 0.3% to 0.5% for overt hypothyroidism[2] and 2% to 3% for subclinical hypothyroidism[3].The American Thyroid Association (ATA), the Endocrine Society, the American Academy of Family Practice (AAFP), the National Institute of Health and the American College of Obstetrics and Gynecology note that untreated overt hypothyroidism is associated with maternal anemia, miscarriage, stillbirth myopathy, congestive heart failure (rare), gestational hypertension, pre-eclampsia, placental abnormalities (placental abruption), low birth weight infants, preterm birth, postpartum hemorrhage and fetal neurocognitive deficits (especially if untreated during the first trimester). Treatment for overt hypothyroidism during pregnancy is levothyroxine with a treatment goal of a serum TSH of <2.5 mIU per L. [4,5,6,7,8]

Tirosint-sol and Drug Characteristics [9]

Tirosint-sol oral solution is a synthetic thyroid hormone. Synthetic T4 is identical to that produced in the human thyroid gland. The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues. Thyroid hormone synthesis and secretion is regulated by the hypothalamic pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin (thyroid-stimulating hormone, TSH), from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, T4 and T3, by the thyroid gland. Circulating serum T3 and T4 levels exert a feedback effect on both TRH and TSH secretion. When serum T3 and T4 levels increase, TRH and TSH secretion decreases. When thyroid hormone levels decrease, TRH and TSH secretion increase. TSH, along with T4 levels and other laboratory and clinical data, is primarily used for both the diagnosis of hypothyroidism and evaluation of levothyroxine therapy adequacy.

Levothyroxine has a molecular weight of 798.85, is 99% protein bound, and has a half-life of 6-7 days. Absorption of orally administered T4 from the gastrointestinal (GI) tract ranges from 40% to 80%. Adverse effects that can occur with levothyroxine therapy and are due to therapeutic overdosage include the following: increased appetite, weight loss, fever, headache, hyperactivity, irritability, tremors, muscle weakness, arrhythmias, elevated blood pressure and pulse, heart failure, myocardial infarction, cardiac arrest and dyspnea.

Levothyroxine and Dose Adjustment during Pregnancy and the Postpartum Period

Due to the risk of adverse maternal and fetal events, maternal hypothyroidism in pregnancy must be corrected as soon as possible by initiating a full replacement dose of levothyroxine (100–150 µg/day or 2.0–2.4 µg/kg body weight/day). Most women with known hypothyroidism need a

[2] Overt Hypothyroidism – is defined as thyroid hormone deficiency with low FT4 and elevated TSH levels >10 mIU/L

[3] Subclinical Hypothyroidism – asymptomatic individuals with elevated TSH and normal FT4
Treatment for overt hypothyroidism and subclinical hypothyroidism is levothyroxine.

[4] Obstetrics and Gynecology. Practice Bulletin No. 148: Thyroid Disease in Pregnancy. Volume1125(4): 996-1005.

[5] American Thyroid Association. http://www.thyroid.org/thyroid-disease-pregnancy/#. Accessed 10/26/2016.

[6] Carney, L, Quilan, J, West, J. Thyroid Disease in Pregnancy. American Family Physician. 2014; 89(4): 273-278.

[7] Stagnaro-Green, et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid. 2011; 21 (10): 1081-1125.

[8] DeGroot, L et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2012; 97(8): 2543-65.

[9] Tirosint-sol (levothyroxine sodium oral solution) Applicant Proposed Labeling

30%–50% increase in the dose of levothyroxine during pregnancy as early as the first four to six weeks gestation. About 25% of pregnant hypothyroid women on levothyroxine have high TSH at their first prenatal visit, which suggests under-replacement. This could, to some extent, be prevented by preconception optimization of levothyroxine dose and, for hypothyroid women planning pregnancy, levothyroxine dose ideally should be adjusted to keep TSH less than 2.5 mIU/L before conception. In patients with known thyroid disease, thyroid function should be checked as soon as the pregnancy is confirmed to adjust the dose of levothyroxine if needed. Thyroid function should be monitored at regular intervals (every 4–6 weeks) to adjust the dose of levothyroxine to keep TSH under 2.5 mIU/L in the first trimester and under 3.0 mIU/L in the second and third trimesters. Patients will need a reduction of their levothyroxine dose after pregnancy. [10]

Current State of the Labeling

- Current labeling for levothyroxine sodium is in the PLR format.
- There is a box warning regarding avoiding the use of thyroid hormones for the treatment of obesity or for weight loss. Larger doses may produce serious or life threatening manifestations of toxicity particularly when given with sympathomimetic amines.
- Contraindications include: Hypersensitivity to glycerol, acute myocardial infarction and uncorrected adrenal insufficiency
- There are no interactions between levothyroxine and contraceptives.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,*"[11] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[12] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience

There are no animal reproduction studies that have been conducted with levothyroxine.

[10] Chakera,et al. Treatment for primary hypothyroidism: current approaches and future possibilities. Drug Des Devel Ther. 2012; 6: 1-11.

[11] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[12] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

Applicant's Clinical Studies/ Pharmacovigilance Database/Review of Literature[13]
The Applicant did not conduct any clinical studies with use of LSOS during pregnancy. Since the application is 505(b)(2) NDA, the Applicant is relying on the Agency's finding of safety and effectiveness for the RLD. In addition, the Applicant notes that they have established bioequivalence between Tirosint Sol and the RLD with Study No. 140161.

IBSA analyzed their post-marketing pharmacovigilance database for all products containing levothyroxine. There were nine case reports associated with the use of levothyroxine in pregnant women and no evidence of harm noted in the infants.

The Applicant performed a Medline review of published literature from 1985 to May 2016 using the search terms "hypothyroidism, levothyroxine, pregnancy." See Appendices B and C for a summary of the main studies that have evaluated the effects of levothyroxine in pregnant women with hypothyroidism.

Overall, the applicant concluded that "levothyroxine use to maintain a condition of euthyroidism in pregnancy allows normal embryo-fetal development, especially of the central nervous system." In addition, "substitutive treatment with levothyroxine was able to lower the chance of miscarriage and premature delivery in euthyroid pregnant women who… had impaired thyroid function… since fetal loss was significantly greater in pregnant women with abnormal TSH value, thyroid function in pregnant women on thyroxine substitution should be monitored early in pregnancy and carefully followed during pregnancy." The reader is referred to the applicant's Clinical Overview for further details of published literature reviewed.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed using the search terms "levothyroxine and pregnancy and fetal malformations in humans/congenital malformations in humans or miscarriage or spontaneous abortion or stillbirth." In addition to the published literature reviewed by the applicant, DPMH reviewed the following studies below.

In a study based on the Swedish Medical Birth Register (Wikner, *et al*.), 9,866 women, who delivered 10, 055 infants between July 1, 1995 and December 31, 2004, were identified as having a prescription for thyroid drugs during pregnancy. Of these, 8,907 reported the use of thyroid hormones in early pregnancy, 5,006 women reported using thyroid hormones later in pregnancy, and 940 women reported no use of thyroid hormone during early pregnancy. Of the women who used thyroid hormones during early pregnancy, 230 (2.6%) had a diagnosis of pre-gestational diabetes and were excluded from further analysis. Concomitant drug use among women using thyroid hormones in early pregnancy, included cardiovascular drugs, systemic corticosteroids, and anti-depressants. Women using thyroid hormones were more likely to be diagnosed with pre-existing hypertension and pre-eclampsia compared to unexposed women. Maternal use of thyroid hormone was not associated with an increased risk of placenta previa, placental abruption, or low birth weight. However, compared to the general population there was a statistically significant risk (OR =1.19, 95% CI 1.06–1.33) for congenital malformations.

[13] IBSA Tirosint-Sol (levothyroxine sodium) oral solution, NDA 206977. 2.5 Clinical Overview.

Congenital malformations with reported increased risk included: 'any cardiovascular defect [OR=1.25, 95% CI 1.05 – 1.49] ' and 'severe kidney malformation [OR 2.04, 95% CI 1.06 - 3.58]'[14] Severe cardiac malformations that trended towards an increased relative risk rate included: Ebstein's anomaly [RR = 2.94, 95% CI 0.07–16.4], endocardial cushion defect [RR = 2.31, 95% CI 1.00 – 16.4] and Tetralogy of Fallot [RR = 2.04 95% CI = 0.88–4.02. Severe kidney malformations were reported in12 infants. Of these 12 infants; one had bilateral and one unilateral kidney agenesis, two had kidney hypoplasia or dysplasia, one horse-shoe kidney, and six cystic kidney (at least three of whom had infantile polycystic kidneys which are genetic). The twelfth infant had an unspecified Potter syndrome (includes renal diseases such as bilateral renal agenesis).[14]

Reviewer comments:
Although the Wikner, et al. study revealed a statistically significant increased rate of congenital cardiac and kidney malformations in infants of women on thyroid substitution during pregnancy, this information does not warrant inclusion in the label. The study reviewed above had several limitations including the duration of drug use and results of thyroid function tests. In addition, women treated for hypothyroidism had a higher risk for hypertension and were more likely to be antihypertensive drugs, some of which are associated with congenital cardiovascular defects. In addition, the neonates with severe kidney malformations had different types of kidney malformations, which makes a causal association to thyroid hormones less likely.

In a cohort analysis (Taylor, *et al*.), 46% of women with hypothyroidism being treated with levothyroxine had a TSH level >2.5 mIU/L. Women with a TSH >2.5mU/L had an increased risk of miscarriage compared with women with TSH 0.2-2.5 mIU/L. The authors noted the importance of improving the adequacy of thyroid hormone replacement in early pregnancy.[15]

Summary
There are no animal reproduction studies that have been conducted with levothyroxine. Untreated hypothyroidism during pregnancy is associated with complications to the mother and the fetus (see "Hypothyroidism and Pregnancy" above). Although there is one study (Wikner, *et al*.) that showed a statistically significant risk for congenital malformations in neonates exposed to thyroid hormone *in utero*, there were several confounders in the study that made an association between levothyroxine and congenital malformations less likely. In addition, there are no studies other than this single large retrospective study that show levothyroxine is associated with congenital malformations, spontaneous abortion or other adverse maternal or fetal outcomes. Therefore, the potential risk of congenital malformations of use of levothyroxine thyroxine in pregnancy does not outweigh the substantial benefit of the drug to prevent the known risk to the mother and fetus. Therefore, DPMH recommends that labeling should indicate that levothyroxine should not be discontinued during pregnancy. Additionally, if hypothyroidism is diagnosed during pregnancy, levothyroxine must be started immediately to prevent adverse maternal and/or fetal outcomes.

[14] Wikner, et al. Maternal use of thyroid hormones in pregnancy and neonatal outcomes. Acta Obstet Gynecol Scand. 2008; 87(6): 617-27.
[15] Taylor, et al. TSH levels and risk of miscarriage in women on long-term levothyroxine: a community-based study. J Clin Endocrinol Metab. 2014; 99(10): 3895-902.

LACTATION

Nonclinical Data

There are no animal lactation studies that have been conducted with levothyroxine.

Applicant's Clinical Studies/ Review of Literature[13]

The Applicant has not conducted any clinical studies with LSOS in lactating women.
The Applicant reviewed published data from Medline and Toxnet (Lactmed) using the search terms "hypothyroidism, levothyroxine, lactation" from 1985 to May 2016. The applicant noted that there was only one study that was conducted in lactating women on exogenous levothyroxine and the results of that study are described below.

In 2002, Van Wassenaer, *et al*.[16] conducted a study and measured thyroid hormone concentration in 118 breast milk samples from 32 mothers of pre-term infants (collection time covered from 5-6 days to 10 weeks after birth); in 10 samples from 10 healthy mothers of term infants (collection time: 1-4 days after birth); and in formula milk. In breast milk, thyroxine concentration ranged between 0.17 mcg/L to 1.83 mcg/L (mean 0.83, SD 0.3 mcg/L), resulting in a maximum T4 supply of 0.3 mcg/kg via ingested breast milk. In formula milk, the T4 concentration was equally low (mean 0.94, SD 0.36 mcg/L). T3 concentrations measured in 10 preterm breast-milk samples ranged from 0.08 mcg/L to 0.18 mcg/L (mean 0.14 mcg/L). The mean T4 concentration in the first week's breast milk from 10 mothers of term infants ranged from 2.11 to 7.41 mcg/L (mean 4.98 mcg/L, SD 1.96). This was almost 6 times more than in the first week's breast milk from 9 mothers of very pre-term infants (mean 0.86, SD 0.38 mcg/L). No significant differences were found in plasma hormone levels between the breast- and formula-fed groups of newborns. The authors concluded that the amount of T4 present in human milk and formula milk is too low to alter the hypothyroxinaemic state of preterm infants.

In LactMed, [11] the "Summary of Use during Lactation" section notes the following:

> "Levothyroxine is a normal component of human milk. Limited data on exogenous replacement doses of levothyroxine during breastfeeding indicate no adverse effects in infants. If levothyroxine is required by the mother, it is not a reason to discontinue breastfeeding. Levothyroxine is recommended treatment for postpartum thyroiditis and tapering of the dose should be avoided when a woman is breastfeeding.[17] Levothyroxine dosage requirement may be increased in the postpartum period compared to pre-pregnancy requirements patients with Hashimoto's thyroiditis.[18]"

[16] van Wessenaer, A., Stulp, M., Valianpour, F., Tamminga, P., Ris, S. C., De Randamie, J., et al. (2002). The quantity of thyroid hormone in human milk is too low to influence plasma thyroid hormone levels in the very preterm infant. *Clinical Endocrinilogy*, 621-7.

[17] Stagnaro-Green A, Abalovich M, Alexander E et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21:1081-125.
[18] Galofre JC, Haber RS, Mitchell AA, Pessah R, Davies TF. Increased postpartum thyroxine replacement in Hashimoto's thyroiditis. Thyroid. 2010;20:901-8.

LactMed also notes the following:

> "Although somewhat controversial, it appears that levothyroxine passes into milk poorly. [19,20,21,22,23] In a study of 56 mothers with thyroid disorders, 50 had hypothyroidism and were being treated with levothyroxine; five mothers had controlled hyperthyroidism with no medications and one had hyperthyroidism treated with a medication. Milk levels of thyroid hormones were free T4 4.5 ng/L, total T4 29.6 mcg/L, free T3 2.3 ng/L and total T3 0.35 mcg/L. The average milk to serum level ratios over the period were free T4 0.32 and total T4 0.3. Levels of free and total T3 and total T4 in milk were positively correlated with their respective plasma levels.[24] Effects of exogenous thyroid hormone administration to mothers on their infants have not been reported.[25,26,27,28,29,30,31] Adequate thyroid hormone serum levels are required for normal lactation. Replacing deficient thyroid levels should improve milk production caused by hypothyroidism. Supraphysiologic doses would not be expected to further improve lactation."

The American Academy of Pediatrics [32] (AAP) states that levothyroxine is compatible with breastfeeding.

The applicant also provided a table comparing the levothyroxine dose administered to newborns with congenital hypothyroidism compared to the maximum T3 and T4 dose obtained from human milk. See the table below for further details.

[19] Sato T, Suzuki Y. Presence of triiodothyronine, no detectable thyroxine and reverse triiodothyronine in human milk. Endocrinol Jpn. 1979;26:507-13.
[20] Varma SK, Collins M, Row A et al Thyroxine, tri-iodothyronine, and reverse tri-iodothyronine concentrations in human milk. J Pediatr. 1978;93:803-6.
[21] Mallol J, Obregon MJ, Morreale de Escobar GM. Analytical artifacts in radioimmunoassay of L-thyroxine in human milk. Clin Chem. 1982;28:1277-82.
[22] Oberkotter LV, Tenore A. Separation and radioimmunoassay of T3 and T4 in human breast milk. Horm Res. 1983;17:11-8.
[23] Koldovsky O. Hormones in milk. Vitam Horm. 1995;50:77-149.
[24] Zhang Q, Lian XL, Chai XF et al. [Relationship between maternal milk and serum thyroid hormones in patients with thyroid related diseases.]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2013;35:427-31.
[25] Bode HH, Vanjonack WJ, Crawford JD. Mitigation of cretinism by breast-feeding. Pediatrics. 1978;62:13-6.
[26] Letarte J, Guyda H, Dussault JH et al. Lack of protective effect of breast-feeding in congenital hypothyroidism: report of 12 cases. Pediatrics. 1980;65:703-5.
[27] van Wassenaer AG, Stulp MR, Valianpour F et al. The quantity of thyroid hormone in human milk is too low to influence plasma thyroid hormone levels in the very preterm infant. Clin Endocrinol. 2002;56:621-7.
[28] Abbassi V, Steinour A. Successful diagnosis of congenital hypothroidism in four breast- fed neonates. J Pediatr. 1980;97:259-61.
[29] Ito S, Blajchman A, Stephenson M et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol. 1993;168:1393-9.
[30] Caplan RH, Wickus GG. Reduced calcitriol requirements for treating hypoparathyroidism during lactation. A case report. J Reprod Med. 1993;38:914-8.
[31] Mungan NO, Kor D, Buyukkurt S et al. Propionic acidemia: A Turkish case report of a successful pregnancy, labor and lactation. J Pediatr Endocrinol Metab. 2016;29:863-6.
[32] American Academy of Pediatrics (2001)

	Highest Reported Concentration in Human Milk (reference)	Maximum Estimated Daily Consumption for Newborn from Exclusive Breastfeeding		Starting Dose for Newborns with Congenital Hypothyroidism[1]	
		mcg/kg	mcg/day for 3kg newborn	mcg/kg	mcg/day for 3kg newborn
T3	1.12 mcg/L (Mizuta *et al*, 1983)	0.168 mcg/kg	0.504 mcg/day	N/A	N/A
T4	29.6 mcg/L (Toxnet, 2014)	4.44 mcg/kg	13.3 mcg/day	10-15 mcg/kg	30-45 mcg/day

In summary, the applicant noted that "levels of T4 and T3 reached in human milk of mothers under levothyroxine therapy are not considered to represent an appreciable risk to the infant. Levothyroxine is in clinical use in young infants at doses exceeding those which would be ingested through breast milk."

DPMH Review of Literature

In addition to the applicant's review of literature, DPMH reviewed data from LactMed,[33] *Medications and Mothers' Milk*[34] Micromedex[35], and published literature in PubMed using the search terms "levothyroxine and lactation" and "levothyroxine and breastfeeding." No reports of adequate and well-controlled studies of levothyroxine use in lactating women were found.

In *Medications and Mother's Milk,*[35] Thomas Hale, a breastfeeding expert, states the following regarding levothyroxine use during lactation:

> "Many studies indicate that minimal levels of maternal thyroid [hormones] are transferred into human milk, and… the amount secreted is extremely low and insufficient to protect a hypothyroid infant even while nursing. The amount secreted after supplementing breastmilk is highly controversial and numerous reports conflict. [One author], Anderson, indicates that levothyroxine is not detectable in breast milk although others using assay methods have shown extremely low levels (4 ng/mL). It generally recognized that some thyroxine will transfer but the amount will be extremely low."

Micromedex notes that "Infant risk is minimal." The American Academy of Pediatrics and the World Health Organization both note that levothyroxine is compatible with breastfeeding.

Summary

Levothyroxine (T4) is a normal component of human milk. Based on limited published data, when levothyroxine is administered to the mother, minimal amounts of the drug are present in

[33] LacMed – http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding CAS Registry Number:51-48-9

[34] Hale, T. (2012). *Medications and Mother's Milk.* Amarillo, Texas Hale Publishing, pg. 650-651.

[35] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 10/26/16.

breast milk, and no adverse effects have been noted in breastfed infants. If levothyroxine is needed by a mother, it is not a reason to discontinue breastfeeding. Therefore, DPMH will revise section 8.2, Lactation, to be consistent with the PLLR format.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There have been no animal studies conducted to evaluate the effects of levothyroxine on fertility.

Applicant's Review of Literature[13]

The Applicant reviewed published data from Medline using the search terms "hypothyroidism, levothyroxine, reproductive potential" from 1985 to May 2016. The applicant noted that there is an association between hypothyroidism and decreased fertility and that "given the adverse effects of hypothyroidism on the (untreated) woman and man and levothyroxine's well-established safety profile, the benefits of using levothyroxine in hypothyroid women and men wishing to conceive clearly outweigh the risks."

DPMH's Review of Literature

In addition to the applicant's search of published literature for information regarding levothyroxine and fertility, DPMH also conducted a review of published literature in PubMed using the following search terms: "levothyroxine and infertility and sperm and humans" and "levothyroxine and infertility and females/males and humans." There is no evidence in the literature to suggest that levothyroxine adversely effects male or female fertility.

Summary

Since there are no human data available on the effect of levothyroxine on male or female fertility Section 8.3, Females and Males of Reproductive Potential, will not be included in Tirosint-SOL labeling.

CONCLUSIONS/RECOMMENDATIONS

Based on the literature review, DPMH has the following recommendations for Tirosint-SOL (levothyroxine oral solution) labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of Tirosint-SOL labeling was formatted in the PLLR format to include the "Risk Summary," "Clinical Considerations," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of Tirosint-SOL labeling was formatted in the PLLR format to include the "Risk Summary" section.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. See Appendix A for the applicant's proposed pregnancy and lactation labeling

DPMH Proposed Tirosint-SOL ((levothyroxine oral solution) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: May require the use of higher doses of Tirosint-Sol during pregnancy. (2.4, 8.1)

FULL PRESCRIBING INFORMATION
2 DOSAGE AND ADMINISTRATION
2.4 Dosing in Specific Patient Populations
Pregnancy

Pregnancy may increase levothyroxine requirements. When hypothyroidism has been diagnosed before pregnancy, serum thyroxine (T_4) levels may decrease and serum thyrotropin (thyroid-stimulating hormone, TSH) levels increase to values outside the normal range during pregnancy. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women taking TIROSINT-SOL should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of TIROSINT-SOL. Since postpartum TSH levels are similar to preconception values, the TIROSINT-SOL dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-8 weeks postpartum.

If hypothyroidism is diagnosed during pregnancy, thyroid function tests (serum TSH) should be normalized as rapidly as possible. Tests should be repeated within 30-40 days and then every 4-6 weeks *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

Experience with levothyroxine use in pregnant women, including data from post-marketing studies, have not reported increased rates of major birth defects or miscarriages *[see Data]*. There are risks to the mother and fetus associated with untreated hypothyroidism in pregnancy. Since thyroid-stimulating hormone (TSH) levels may increase during pregnancy, TSH should be monitored and TIROSINT-SOL dosage adjusted during pregnancy *[see Clinical Considerations]*. There are no animal studies conducted with levothyroxine during pregnancy. Levothyroxine should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Maternal hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth, gestational hypertension, and

premature delivery. Untreated maternal hypothyroidism may have an adverse effect on fetal neurocognitive development.

Dose Adjustments During Pregnancy and the Postpartum Period
Pregnancy may increase levothyroxine requirements. Serum TSH levels should be monitored and the TIROSINT-SOL dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the TIROSINT-SOL dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-8 weeks postpartum. [*see Dosage and Administration (2.4)*].

Data
Human Data
Levothyroxine is approved for use as a replacement therapy for hypothyroidism. There is a long experience of levothyroxine use in pregnant women, including data from post-marketing studies that have not reported increased rates of fetal malformations, miscarriages or other adverse maternal or fetal outcomes with drug use in pregnant women.

Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent *in utero* hypothyroidism.

8.2 Lactation
Risk Summary
Limited published studies report that levothyroxine is present in human milk. However, there is insufficient information to determine the effects of levothyroxine on the breastfed infant and no available information on the effects of levothyroxine on milk production. Adequate levothyroxine treatment during lactation may normalize milk production in hypothyroid lactating mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TIROSINT-SOL and any potential adverse effects on the breastfed infant from TIROSINT-SOL or from the underlying maternal condition.

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/s/

JACQUELINE A SPAULDING
11/04/2016

MIRIAM C DINATALE
11/04/2016

LYNNE P YAO
11/10/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 8, 2016
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Ramachandra Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TIROSINT-SOL (levothyroxine sodium)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 206977
Applicant:	IBSA Institut Biochimique SA

1 INTRODUCTION

On February 26, 2016, IBSA Institut Biochimique submitted for the Agency's review an Original New Drug Application for TIROSINT-SOL (levothyroxine sodium) oral solution. The purpose of the submission is to seek approval for the oral solution form for TIROSINT (levothyroxine sodium) capsules which are currently approved.

TIROSINT-SOL (levothyroxine sodium) oral solution 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 radioline therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on October 14, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TIROSINT-SOL (levothyroxine sodium) oral solution.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 7, 2016.

2 MATERIAL REVIEWED

- Draft TIROSINT-SOL (levothyroxine sodium) oral solution PPI and IFU received on February 26, 2016, and received by DMPP and OPDP on October 29, 2016.
- Draft, TIROSINT-SOL (levothyroxine sodium) oral solution Prescribing Information (PI) received on February 26, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 29, 2016.
- DMPP review of TIROSINT (levothyrorine sodium) capsules labeling dated September 9, 2015.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
11/08/2016

MEENA RAMACHANDRA
11/08/2016

SHAWNA L HUTCHINS
11/08/2016

LASHAWN M GRIFFITHS
11/08/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 7, 2016
Requesting Office or Division:	Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number:	NDA 206977
Product Name and Strength:	Tirosint-SOL (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
Product Type:	Single-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Institut Biochimique SA (IBSA)
Submission Date:	February 26, 2016, and July 15, 2016
OSE RCM #:	2016-511
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader (Acting):	Hina Mehta, Pharm.D.
DMEPA Deputy Director	Lubna Merchant, M.S., Pharm.D.

1 REASON FOR REVIEW

Institut Biochimique SA submitted NDA 206977 for Tirosint-Sol (levothyroxine) oral solution on February 26, 2016. Thus, the Division of Metabolism and Endocrinology Products requested DMEPA review the proposed carton and container labeling, as well as prescribing information (PI) for areas of vulnerability that could lead to medication errors.

Of note, the container (ampule) labels were previously reviewed by DMEPA in 2013 under IND 115023 and were found acceptable. However, at that time no carton labeling were submitted.

1.1 REGULATORY HISTORY

Tirosint was approved under NDA 021924 as 0.025 mg, 0.05 mg, 0.075 mg, 0.1 mg, 0.125 mg, 0.15 mg, 0.112 mg, 0.137 mg, and 0.088 mg oral capsules on October 13, 2006. Tirosint was also approved under NDA 022121 as a 0.013 mg oral capsule on August 1, 2007. The same Applicant is submitting a new drug application (NDA) for the oral solution formulation which is the basis of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	C
Other	N/A
Labels and Labeling	E

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed carton labels, container (ampule) labels, and prescribing information (PI) for Tirosint-SOL to identify deficiencies that may lead to medication errors and other areas of improvement. DMEPA identified areas in the labels and labeling that can be improved to increase the readability and prominence of important information.

We also conducted a gap FAERS search to identify whether any medication errors occurred with the RLD drug, TIROSINT from the time of our last review which utilized a FAERS search (OSE Review 2015-1294) dated, July 30, 2015. We did not identify any new post-market medication error reports associated with the labels and labeling for Tirosint, which may be relevant to Tirosint-SOL.

DMEPA identified areas in the labels and labeling that can be improved to increase the readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the container label and carton labeling to address these deficiencies.

We sent a request to the Applicant on August 18, 2016 for samples of the containers. The Applicant stated they would not be able to send the samples until October 2016. Our comments are based on pictures of the container sent by the applicant on August 24, 2016 (see Appendix E). We may have additional comments once we receive and review the samples.

CONCLUSION & RECOMMENDATIONS

DMEPA has identified areas of improvement for carton and container labels and labeling in order to enhance readability and to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR BSA INSTITUT BIOCHIMIQUE SA

We recommend the following be implemented prior to approval of this NDA:

A. All Carton Labels:

1) Revise the "13 mcg (b) (4) mL" from the concentration strength to read as "13 mcg/mL". Revise this on the carton of each strength proposed.

2) The NDC numbers are currently denoted as a place-holder (i.e. XXXXX-XXXX-XX), please submit the actual NDC numbers once finalized.

B. **Over-The Pouch Container Labels**:

1) The drug barcode is not present on the over-the-pouch container labels. The barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual [PACKAGE] as required per 21CFR 201.25(c)(2).

2) See A 1-2 above

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for TIROSINT-SOL that Institut Biochimique SA submitted on February 26, 2016 and July 15, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for TIROSINT-SOL and the Listed Drug		
Product Name	**TIROSINT-SOL**	**TIROSINT**
Initial Approval Date	N/A	October 13, 2006
Active Ingredient	Levothyroxine sodium	Levothyroxine sodium
Indication	Hypothyroidism and pituitary Thyrotropin Stimulating Hormone suppression	Hypothyroidism and pituitary Thyrotropin Stimulating Hormone suppression
Route of Administration	Oral	Oral
Dosage Form	Oral Solution	Oral Capsule
Strength	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	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
Dose and Frequency	Individualized dose once daily	Individualized dose once daily
How Supplied	TIROSINT-SOL (levothyroxine sodium) oral solution is clear, colorless to slightly yellow solution supplied in a 1 mL white, non-transparent, unit-dose ampule. TIROSINT-SOL is supplied in boxes of 30 ampules, consisting of 6 pouches, each containing a strip of 5 unit-dose ampules. Each dosage strength is associated with a distinct color. **Table 7: TIROSINT-SOL Packaging Description** **Strength (mcg) Color* Box NDC Pouch NDC** 13 Green xxxxx-xxx-30 xxxxx-xxx-05 25 Orange xxxxx-xxx-30 xxxxx-xxx-05 50 White xxxxx-xxx-30 xxxxx-xxx-05 75 Purple xxxxx-xxx-30 xxxxx-xxx-05 88 Olive xxxxx-xxx-30 xxxxx-xxx-05 100 Yellow xxxxx-xxx-30 xxxxx-xxx-05 112 Rose xxxxx-xxx-30 xxxxx-xxx-05 125 Brown xxxxx-xxx-30 xxxxx-xxx-05 137 Turquoise xxxxx-xxx-30 xxxxx-xxx-05 150 Blue xxxxx-xxx-30 xxxxx-xxx-05 175 Lilac xxxxx-xxx-30 xxxxx-xxx-05	TIROSINT (levothyroxine sodium) capsules are amber-colored, round/biconvex capsules that contain a viscous amber-colored liquid. They are supplied as follows: Boxes of 28 capsules, consisting of 4 blisters with 7 capsules each. The dosage strength on each box is clearly identified in several locations, and is associated with a distinct color. The color of the circles on the blister is the same color as on the box. Each blister pack contains 7 capsules placed in individual cavities labeled with the dosage strength, the

	200 Pink xxxxx-xxx-30 xxxxx-xxx-05	product name (TIROSINT), and an abbreviation for the day of the week on which the capsule is taken. **Table 7: TIROSINT Packaging Description** **Strength (mcg) Color* NDC** 13 Green 24090-490-84 25 Orange 24090-491-84 50 White 24090-492-84 75 Purple 24090-493-84 88 Olive 24090-494-84 100 Yellow 24090-495-84 112 Rose 24090-496-84 125 Brown 24090-497-84 137 Turquoise 24090-498-84 150 Blue 24090-499-84
Storage	Store TIROSINT-SOL in the original container (closed pouch) at 25°C (77°F); excursions permitted to 15°-30°C (59-86°F) [See USP Controlled Room Temperature]. Use TIROSINT-SOL oral solution within 15 days after opening the pouch. Keep the ampules in the pouch until ready to use.	Store at 25°C (77°F); excursions permitted to 15°-30°C (59-86°F) [See USP Controlled Room Temperature]. TIROSINT capsules should be protected from heat, light and moisture.
Container Closure	white, non-transparent, low-density polyethylene (LDPE) unit-dose ampules.	amber-colored, round/biconvex capsules that contain a viscous amber-colored liquid

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 15, 2016, we searched the L:drive and AIMS using the terms, TIROSINT, and LEVOTHYROXINE ORAL SOLUTION to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 5 previous review and our recommendations were implemented[1].

Control Number	Recommendation(s)
2011-1534 (TIROSINT)	- Revise the proposed colors/color scheme to more closely match the colors of this product line (i.e., lilac for 175 mcg and pink for 200 mcg). - Change the color for the strength statement (white) as this lacks sufficient contrast against background colors (lilac, pink) making them difficult to read - Add identifying markings to each capsule to reflect the different strengths
2012-1884 (TIROSINT)	- Add a darker ink marking on the capsules to make imprint more visible - Use imprint markings which are not prone to mix-ups - Use different letters for imprint markings which do not overlap with other product's imprints
2016-1020 (LEVOTHYROXINE SODIUM ORAL SOLUTION)	- DMEPA concluded that the proposed label, labeling for Levothyroxine oral solution IND 115023 were acceptable from medication error perspective
2014-50	- Add imprint codes for each strength to the table in the How Supplied/Storage and Handling section in the Prescribing Information
2015-1294	- No recommendations for TIROSINT capsules. We found the label and labeling acceptable.

APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

C.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on July 15, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[1]

Table 3: FAERS Search Strategy	
Date Range	**FDA Rcvd Date From:** 20150701 (from the last FAERS search) **FDA Rcvd Date To:** 20150715
Product	**TIROS*** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT] **Additional terms:** Product Dosage Form Confusion [PT] Product Label Confusion [PT]

C.2 Results

Our search identified 14 cases; no cases of medication errors which could be addressed by label and labeling revisions. We excluded all 14 cases because they described adverse events such as complaints of jitteriness and intentional dose omission or they were not relevant to TIROSINT.

[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

C.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On August 2, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Joint Commission QAA Community QAA Acute Care PA Patient Safety Nursing Newsletter Community Newsletter Acute Care Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Tirosint

D.2 Results

No newsletters regarding label and labeling errors related to Tirosint have been identified.

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following TIROSENT-SOL labels and labeling submitted by Institut Biochimique SA on February 26, 2016 and July 15, 2016.

- Carton labeling
- Container (Ampule) Labels
- Over-The-Pouch Labels
- Photograph of the samples

E.2 Label and Labeling:

Carton Labels:


Draft Carton Labels.pdf

Container Labels:


Draft container.pdf

Over-The-Pouch Labels:


Draft Over-Pouch Labels.pdf

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Photograph of Samples:

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

/s/

LEEZA RAHIMI
09/07/2016

HINA S MEHTA
09/07/2016

LUBNA A MERCHANT
09/07/2016