CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206977Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME 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:	May 18, 2016
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
Rx or OTC:	RX
Applicant/Sponsor Name:	Institut Biochimique SA
Panorama #:	2016-2996070
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Tirosint-SOL, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and the appendix respectively. The Applicant did not submit an external name study for this proposed proprietary name

1.1 REGULATORY HISTORY

The proposed root name, 'Tirosint', for the approved oral capsule product, levothyroxine sodium, was reviewed in OSE Review# 06-0015[1], dated November 30, 2005. The review did not recommend the use of the proprietary name, Tirosint, for NDA 21924; however, the NDA was approved under the proprietary name 'Tirosint' on October 13, 2006.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 9, 2016 proprietary name submission. This NDA proposes the oral solution formulation for levothyroxine sodium with the same strength per mL as Tirosint (NDA 21924) oral capsules.

- Intended Pronunciation: tee-row-sent-sōl
- Active Ingredient: levothyroxine sodium
- Indication of Use: Hypothyroidism and pituitary Thyrotropin Stimulating Hormone suppression
- Route of Administration: oral
- Dosage Form: solution
- 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
- Dose and Frequency: 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.
- 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

[1] Bridges T. Proprietary Name Review for Tirosint (NDA 21924). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2005 NOV 30. 29 p. OSE RCM No.: 2006-0015.

Temperature]. Use TIROSINT-SOL oral solution within 15 days after opening the pouch. Keep the ampules in the pouch until ready to use.

- Container and Closure Systems: white, non-transparent, (b) (4) unit-dose ampules.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Metabolism and Endocrinology (DMEP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[2].

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Tirosint-SOL, is derived from: Tiro is the abbreviation for the Italian word, Tiroide (which translates to Thyroid in English) and Sint is the abbreviation for the Italian word, Sintetica (which translates to Synthetic in English). SOL is the abbreviation for Solution. An analysis of the proposed root name and appropriateness of the modifier is discussed in Section 2.2.6.

2.2.3 FDA Name Simulation Studies

Ninety-three practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, April 1, 2016 e-mail, the Division of Metabolism and Endocrinology Products (DMEP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

[2]USAN stem search conducted on 4/11/16.

2.2.5 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving ***Tirosint*** that would be relevant for this review.

Table 2. FAERS Search Strategy	
Search Date	March 18, 2016
Drug Name	Tirosint [product name]
Date Limits	10/13/2006 to 3/1/2016
Search Date	April 20, 2016
Drug Name	Tis-U-Sol [product name]
Date Limits	1/1/2010 to 4/20/2016
Event (MedDRA Terms)	**DMEPA Official Proprietary Name Review Search Terms Event List:** Product name confusion (PT) Medication error (PT) Intercepted medication error (PT) Drug dispensing error (PT) Intercepted drug dispensing error (PT) Circumstance or information capable of leading to a medication error (PT)

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, one report was not included in the final analysis for the following reasons: Not related to name confusion.

Following exclusions, the search yielded no relevant cases.

2.2.6 Analysis of the Root Name and Proposed Modifier SOL

Tirosint is currently marketed levothyroxine sodium oral capsules available in 13 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, and 150 mcg and administered once daily. The proposed strengths of 175 mcg and 200 mcg are pending approval. We have not identified any cases of name confusion related to the root name, Tirosint. The proposed product also contains levothyroxine sodium as the active ingredient. Therefore, the root name Tirosint is appropriate for this product since providers are already familiar with Tirosint containing levothyroxine sodium.

The modifier, 'Sol' is used to differentiate the oral solution formulation from the oral capsule formulation. The modifier "Sol", although not commonly used, has been used before to denote "solution" (e.g. Tis-U-Sol, NDA 18508). Search of FAERS for name confusion involving Tis-U-Sol did not identify any cases. Therefore, the modifier "Sol" is acceptable for this product since it is an oral solution.

Although multiple dosage forms for a product are typically managed under a single proprietary name, we note that the applicant requested a modifier "sol" for the solution dosage form. We requested input from the clinical team to determine if the proposed oral solution and the currently marketed oral capsules could be managed with a single proprietary name and under single prescribing information (PI). The medical officer stated that due to the differing patient population (children under the age of 6), levothyroxine being a narrow therapeutic index drug, and complex dosing instructions and risk of underdose if the instructions are not explicitly followed, that they would prefer to have a separate proprietary name and PI.

We considered the points raised by the clinical team in determining the acceptability of this name. We also note that the two highest doses proposed for the oral solution (i.e. 175 mcg/mL and 200 mcg/mL) are pending approval for the oral capsule formulation and are not in the currently approved PI for Tirosint oral capsules.

We note that omission and oversight of a modifier is cited in literature as a common cause of medication error[3]. Postmarketing experience shows that the introduction of product line extensions result in medication errors if the modifier is omitted and the product characteristics are similar or overlap. If the modifier is dropped, the oral capsule formulation of Tirosint would be dispensed and lead to possible delay of treatment. However, as with products with multiple dosage forms managed under a single proprietary name, the prescriber would need to specify the intended dosage form on the prescription even if the modifier is dropped. Therefore, for the aforementioned reasons listed, we find that the proprietary name 'Tirosint-SOL,' although not free from the risk of error, offers a safe approach to naming this product.

2.2.7 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to DMEP via e-mail on May 6, 2016. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from DMEP on May 12, 2016, they stated no additional concerns with the proposed proprietary name, Tirosint-SOL.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Deveonne Hamilton-Stokes, OSE project manager, at 301-796-2253.

[3] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

3.1 COMMENTS TO THE APPLICANT

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

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

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

APPENDICES

Appendix A1: 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 B: Prescription Simulation Samples and Results

Figure 1. Tirosint-SOL Study (Conducted on 3/21/2016)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Tirosint-Sol 200mcg/mL 1mL po daily Outpatient Prescription: Tirosint-Sol 25mcg/mL 1 mL PO q day #30	Tirosint-SOL 25 mcg/mL 1 mL PO once daily #30

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Tirosint SOL
286 People Received
Study
93 People Responded

Total	**33**	**32**	**28**	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
FIROSINT SOL	0	0	1	1
JIROSINT-SAL	0	0	1	1
LINOSINT SOL	1	0	0	1
LIROSENT SOL	0	0	1	1
LIROSINT SOL	0	0	2	2
LIROSINT-SOL	1	0	5	6
LIROSINT-SOL 200 MCG/ML	0	0	1	1
SOL	0	1	0	1
TEROCENT FOAM	0	1	0	1
TEROCENT SOL	0	1	0	1
TEROCYNT SOUL	0	1	0	1
TEROSENT SOL	0	1	0	1
TEROSINSOL	0	1	0	1
TEROSINT FOAM	0	1	0	1
TEROSINT SOL	0	1	0	1
TEROSYNT SOL	0	1	0	1

TEROSYNTH SOL	0	1	0	1
TEROSYNTH SOUL	0	1	0	1
TERS SOL	0	1	0	1
THEROSENTSOL	0	1	0	1
TIRONSINT-SOL	1	0	0	1
TIROSENT SOL	0	2	0	2
TIROSENT SOLE	0	1	0	1
TIROSENT-SOL	0	1	0	1
TIROSINT SAL	0	0	1	1
TIROSINT SOL	2	4	2	8
TIROSINT SOL 25MCG/ML	1	0	0	1
TIROSINT SOLUNTION	1	0	0	1
TIROSINT SOLUTION	1	0	2	3
TIROSINT-SAL	1	0	1	2
TIROSINT-SOL	21	0	11	32
TIROSINT-SOL 25 MCG/ML	1	0	0	1
TIROSINT-SOL 25MCG/ML	1	0	0	1
TIROSIS SOL 25 MCG/ML	0	1	0	1
TIROSNT-SOL	1	0	0	1
TIROSYN SOL	0	1	0	1
TIROSYNT SOL	0	1	0	1
TROSENT SOL	0	2	0	2
TYROSENT SOL	0	3	0	3
TYROSENTSOL	0	1	0	1
TYROSINE SOL	0	1	0	1
TYROSYNTH SOUL	0	1	0	1

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/s/

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