

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-121**

**CHEMISTRY REVIEW(S)**



**NDA 22-121**

**TIROSINT**  
**(levothyroxine sodium) capsules**  
**13 mcg strength**

**Institut Biochimique SA (IBSA)**

**Sheldon Markofsky, Ph.D.**

**Division of Metabolism and Endocrine Drug Products (HFD-510)**

**and**

**Office of New Drug Quality Assessment I**  
**Branch II**

**File: n22121Rev#1**

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Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 22-121
2. REVIEW #: 1
3. REVIEW DATE: 29-March-2007
4. REVIEWER: Sheldon Markofsky, Ph.D.

**5. PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original for NDA 22-121)	18-Oct-2006
NDA (Original for NDA 21-924)	30-Nov-2005
Amendment to NDA 21-924	30-March-2006
Amendment to NDA 21-924	27-June-2006
Amendment to NDA 22-121	16-Feb-2007
Amendment to NDA 22-121	13-March-2007
IR Letter	27-March-2007

**6. SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment to NDA 22-121 <sup>1</sup>	16-Feb-2007
Amendment to NDA 22-121 <sup>2</sup>	13-March-2007

- 1) The 2-16-07 amendment provides Chemistry related information to support the 13 mcg Tirosint capsules.
- 2) The 3-13-07 amendment allows information from NDA 21-924 to support NDA 221-121.

**7. NAME & ADDRESS OF APPLICANT:**

Name: Institut Biochimique SA (IBSA)

Address: Via Del Piano  
Casella Postale 266  
CH-6915  
Pambio-Noranco  
Switzerland

Representative: Clarence E. Jones, Ph.D.  
8602 Mossford Drive  
Huntington Beach, CA 92646

Telephone: 714-963-0078



## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tirosint
- b) Non-Proprietary Name: levothyroxine sodium capsules
- c) USAN Name: levothyroxine sodium
- d) Code Name/# (ONDQA only): T<sub>4</sub> Capsules
- e) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 6
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

(The firm claims bioequivalence to Synthroid (Levothyroxine Sodium Tablets, USP))

## 10. PHARMACOL. CATEGORY: Hypothyroidism/Pituitary TSH Suppression

## 11. DOSAGE FORM: Soft Gelatin Capsule

## 12. STRENGTH/POTENCY: 13 mcg

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OT15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

.Established (INN, USAN) Name: Levothyroxine Sodium

.Inverted IUPAC Name: \_\_\_\_\_

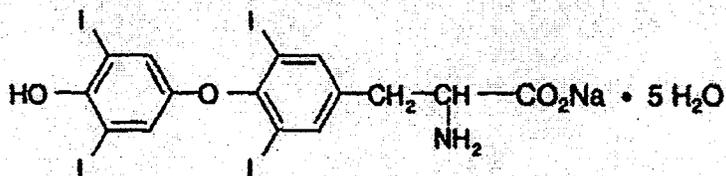
.Molecular formula: C<sub>15</sub>H<sub>10</sub>I<sub>4</sub>NNaO<sub>4</sub>·5H<sub>2</sub>O

.Molecular weight:  
material)

798.86 g/mol (anhydrous)

## Chemistry Review Data Sheet

Chemical structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
<del>1</del>	II	<del>_____</del>	Levothyroxine sodium	3	Adequate*	2-14-05	Reviewed by M Shaikh (Review # 7)
<del>2</del>	III	<del>_____</del>		3	Adequate*	7-22-05	Reviewed by Craig Bertha
<del>3</del>	III	<del>_____</del>		3	Adequate*	5-22-02	Reviewed by Lorenzo Rocca

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed.)

\* The recommendations are for NDA 21-924 and are applicable to this NDA.



## Chemistry Review Data Sheet

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,039	Clinical protocol for bioavailability studies (6-7-04)

## 18. STATUS:

## ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	3-8-07	
Pharm/Tox	N/A		
Clinical Pharm	Acceptable <sup>1</sup>	8-30-06	Sang Chung
LNC	N/A		
Methods Validation	Acceptable <sup>1</sup>	8-31-06	S. B. Markofsky
DMETS	N/A		
EA	Acceptable <sup>1</sup>	5-2-06	Markofsky (Chem. Rev. #1)
Microbiology	Acceptable <sup>1</sup>	4-12-06	Anastasia Lolos

1) The recommendations are for NDA 21-924 and are applicable to this NDA.

19. ORDER OF REVIEW: N/A (OGD Only)

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On Original

The Executive Summary

## The Chemistry Review for NDA 22-121

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved.

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substances

##### 1) Drug Product

*Note:*

*The 13 mcg strength of Tirosint is essentially identical to the 12.5 mcg strength of the drug product that was approved from a Chemistry point of view for NDA 21-924. However, since a 12.5 mcg strength would be distinguished from a 125 mcg strength by only a decimal point, a 13 mcg strength was suggested by the clinical division to avoid possible dosing errors.*

The drug product, which has the proprietary name Tirosint and the established name levothyroxine sodium capsules, is used for treatment of hypothyroidism and pituitary TSH suppression. The dosage form is an immediate-release oral soft gelatin capsule whose core contains levothyroxine sodium dissolved in glycerin. Although these capsules are a new dosage form for levothyroxine sodium, the firm claims bioequivalence to Synthroid (levothyroxine sodium tablets, USP). Tirosint is available in 7 strengths ranging from 13 to 150 mcg per capsule. The firm has proposed to package the drug product in aluminum-backed blister packs (7 capsules per pack and 5 blister packs per carton).

Since Tirosint consists of a freely soluble levothyroxine solution inside of a gelatin shell, the active ingredient dissolves suddenly and very rapidly in a somewhat random fashion. Accordingly, the generation of dissolution profiles is not appropriate for this dosage form; and only a                      specification will be used to monitor these capsules.

## 2) Drug Substance

The drug substance, levothyroxine sodium, USP, is manufactured by                      and the relevant CMC issues related to the manufacture of this material are described in DMF                     . This DMF has previously been reviewed and found adequate to support other levothyroxine sodium drug products and is also deemed satisfactory for Tirosint. The drug substance is stable for five years under normal storage conditions.

### B. Description of How the Drug Product is Intended to be Used

The typical dose of Tirosint ranges from 13 to 200 mcg, to be administered once daily. Some patients will need to take two capsules of levothyroxine sodium in order to obtain a daily dose of greater than 150 mcg or for doses such as 38, 68, or 88 mcg etc. Levothyroxine sodium has a narrow therapeutic index, and the correct dose is tailored to the individual patient, and is typically re-evaluated 1-2 times per year. The tablet strengths of 25, 50, 75, 100, 125 and 150 mcg per capsule were previously approved for NDA 21-924, and the 13 mcg strength is the subject of this NDA (22-121). The stability data, provided in NDA 21-924, support an 18 month expiry (25 °C with excursions permitted between 15 °C and 30 °C) for the capsules packaged in blister packs, and, indeed an 18 month expiry is also granted for the 13 mcg capsules.

### C. Basis for Approvability or Not-Approval Recommendation

The NDA can be approved from a Chemistry point of view on the following basis, which is mostly derived from NDA 21-024:

- Adequate information was provided in DMF                      for the synthesis, purification and controls of the drug substance
- Adequate manufacturing information to support the proposed to-be-marketed drug product

- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability package to support the recommended expiry period of the drug product
- The relevant Chemistry Manufacturing & Control (CMC) related facilities have received an acceptable Establishment Inspection Report.

### **III. Administrative**

#### **A. Reviewer's Signature**

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)

#### **B. Endorsement Block (OGD only)**

N/A

#### **C. CC Block (OGD only)**

N/A

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10 Page(s) Withheld

2 Trade Secret / Confidential

       Draft Labeling

       Deliberative Process