CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-924

CHEMISTRY REVIEW(S)

MEMORANDUM

FROM: Sheldon Markofsky, Ph.D.
Review Chemist (Office of New Drug Quality Assessment I, Branch II)

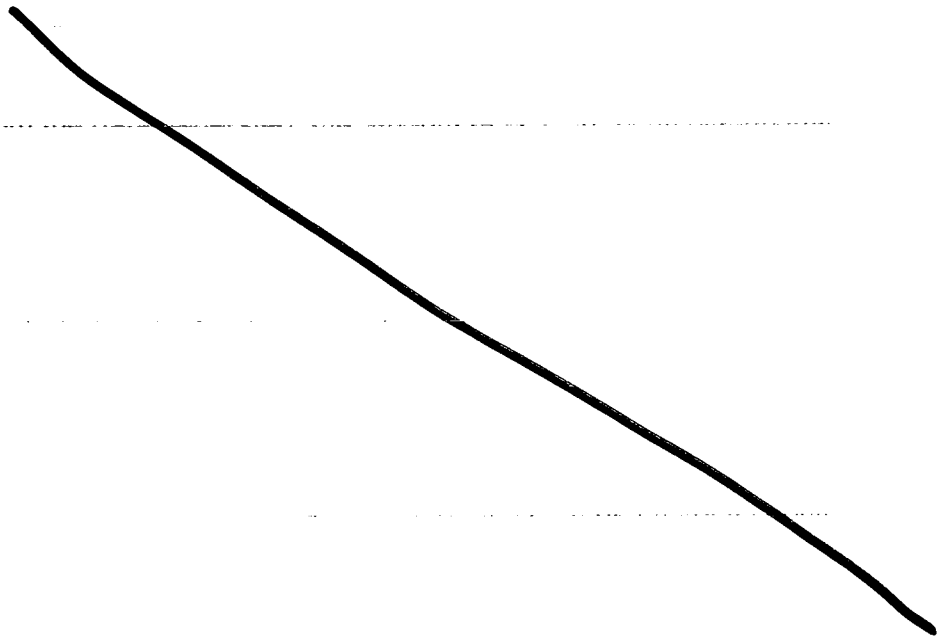
Date: 9-21-06

To: NDA 21-924 for Tirosint (levothyroxine sodium) capsules
Subject: NDA 21-924 amendment, dated 8-29-06

It was previously reported in Chemistry Review #2 that from a Chemistry, Manufacturing, and Controls (CMC) point of view, NDA 21-924 can be approved, pending an acceptable cGMP status for the relevant manufacturing and testing facilities. This 8-29-06 amendment does not change this recommendation. The amendment merely adds additional information which is described below:

1) The amendment provided drug-product-dissolution-information which had already been examined by the Clinical Pharmacology Reviewer, Sang Chung, in his 8-30-06 review.

2) The amendment provided chromatogram traces and related information to show the suitability of the firm's method for the determination of impurities and degradants in the drug product.



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/s/

Sheldon Markofsky
9/21/2006 02:37:43 PM
CHEMIST

NDA 21-924

TIROSINT
(levothyroxine sodium) capsules

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: n21924Rev#2c

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A APPENDICES ..... N/A

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II. List Of Deficiencies To Be Communicated ..... N/A

Chemistry Review Data Sheet

1. NDA 21-924

2. REVIEW #: 2

3. REVIEW DATE: 31-Aug-2006

4. REVIEWER: Sheldon Markofsky, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA (Original)	30-Nov-2005
IR Letter & Filing Communication	10-Feb-2006
Chemistry Review #1	04-May-06
Discipline Review Letter	18-May-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA Original	30-Nov-2005
Amendment[a]	30-March-2006
Amendment[b]	27-June-2006

a) The 3-30-06 amendment provides responses to the IR Letter & Filing Communication, dated 2-10-06
b) The 6-27-06 amendment provides responses' to the Discipline review Letter, dated 5-18-06

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_4 Capsules
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- 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: 12.5, 25, 50, 75, 100, 125 & 150 mcg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OT

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

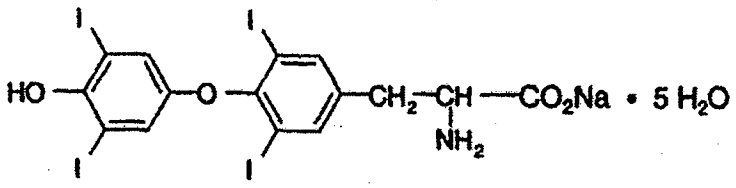
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

.Est ablished (INN, USAN) Name: Levothyroxine Sodium
.In verted IUPAC Name: [redacted]

.M olecular formula: $C_{15}H_{10}I_4NNaO_4.5H_2O$
.M olecular weight: [redacted] and 798.86 g/mol (anhydrous material)

Chemistry Review Data Sheet

Chemical structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Levothyroxine sodium	3	Adequate	2-14-05	Reviewed by M Shaikh (Review # 7)
[redacted]	III	[redacted]	[redacted]	3	Adequate	7-22-05	Reviewed by Craig Bertha
[redacted]	III	[redacted]	[redacted]	3	Adequate	5-22-02	Reviewed by Lorenzo Rocca

[1] 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")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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	Pending		
Pharm/Tox	N/A		
Clinical Pharm	Acceptable	8-30-06	Sang Chung
LNC	N/A		
Methods Validation	Acceptable	8-31-06	S. B. Markofsky
DMETS	Pending		
EA	Acceptable	5-2-06	Markofsky (Chem. Rev. #1)
Microbiology	Acceptable	4-12-06	Anastasia Lolas

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

The Executive Summary

The Chemistry Review for NDA 21-924

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved, pending an acceptable cGMP status for the relevant manufacturing and testing facilities.

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

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). The drug product is available in 7 strengths ranging from [redacted] to 150 mcg per capsule. The firm has proposed to package Tirosint 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 [redacted] specification will be used to monitor these capsules.

2) Drug Substance

The drug substance, levothyroxine sodium, USP, is manufactured by [redacted], and the relevant CMC issues related to the manufacture of this material are described in DMF [redacted] 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 12.5 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 37.5, 67.5, or 87.5 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 proposed tablet strengths are 12.5, 25, 50, 75, 100, 125 and 150 mcg per capsule. The stability data support an 18 month expiry (25 ^{0}C with excursions permitted between 15 ^{0}C and 30 ^{0}C) for the capsules packaged in blister packs, and, indeed an 18 month expiry is granted.

C. Basis for Approvability or Not-Approval Recommendation

The application can be approved pending a satisfactory Establishment Inspection Report. If the Inspection report is deemed satisfactory, the NDA can be approved from a Chemistry point of view on the following basis:

- Adequate information was provided in DMF [redacted] 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

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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Withheld Track Number: Chemistry- 1

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/s/

Sheldon Markofsky
8/31/2006 04:06:28 PM
CHEMIST

Blair Fraser
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CHEMIST

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TIROSINT
(levothyroxine sodium) capsules
NDA 21-924

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Institut Biochimique SA (IBSA)
Via Del Piano
Casella Postale 266
CH-6915
Pambio-Noranco
Switzerland

Indication: Hypothyroidism and pituitary thyroid-stimulating hormone (TSH) suppression

Presentation: Immediate-release soft gelatin capsules are

provided in seven strengths (12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg and 150 mcg per capsule) and

packaged in aluminum-backed blister packs (7 capsules per pack [redacted]). The product is packaged in different-colored blister packs to distinguish the various strengths of the capsules.

EER Status: **Pending**

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(b) 2-May-2006
Microbiology – Acceptable 12-Apr-2006
Methods Validation – Acceptable 31-Aug-2006

Original Submission: 30-Nov-2005
Amendment: 30-Mar-2006 (Responses to Information Request)
27-Jun-2006 (Responses to Discipline Review letter)

Post-Approval Agreements: None

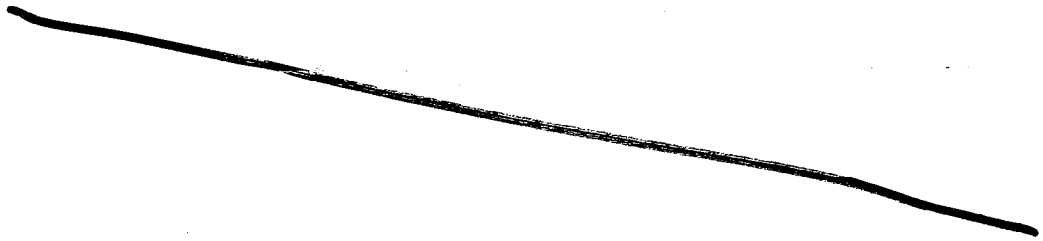
Drug Substance:

The drug substance, levothyroxine sodium, has a molecular formula: $C_{15}H_{10}I_4NNaO_4.5H_2O$, a molecular weight of [redacted] and compendial monographs (USP and Ph. Eur.). Manufactured by [redacted] the relevant CMC issues related to the manufacture of this material are described in DMF [redacted] This DMF was found adequate for a

tablet product on 14-FEB-2005 (Chem. Review #7) and there has been no revision since. The drug substance is stable for five years under normal storage conditions.

Conclusion: Drug substance is acceptable.

Drug Product:



Adequate stability data were provided to support the proposed expiration dating of 18 months for drug product packaged in the proposed blister packs and stored at 25°C.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval** pending satisfactory cGMP status

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
9/1/2006 06:05:46 AM
CHEMIST

NDA 21-924

TIROSINT
(levothyroxine sodium soft gelatin capsules)

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: n21924Rev#1e

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P DRUG PRODUCT ..... pp. 12

A APPENDICES ..... N/A

R REGIONAL INFORMATION ..... N/A

II. List Of Deficiencies To Be Communicated 57

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Chemistry Review Data Sheet

1. NDA 21-924

2. REVIEW #: 1

3. REVIEW DATE: 02-May-2006

4. REVIEWER: Sheldon Markofsky, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA (Original)	30-Nov-2005
IR Letter & Filing Communication	10-Feb-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA Original	30-Nov-2005
Amendment[a]	30-March-2006

a) The 3-30-06 amendment provides responses to the IR Letter & Filing Communication, dated 2-10-06

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 soft gelatin capsules
c) USAN Name: : levothyroxine sodium

d) Code Name/# (ONDQA only): T_4 Soft Capsules
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- 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: 12.5, 25, 50, 75, 100, 125 & 150 mcg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OT

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

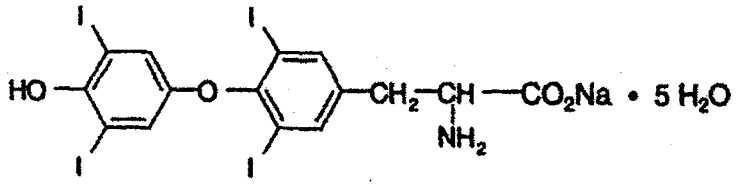
.Est ablished (INN, USAN) Name: Levothyroxine Sodium

[redacted]

.Mo lecular formula: $C_{15}H_{10}I_4NNaO_4.5H_2O$
.Mo lecular weight: [redacted] 798.86 g/mol (anhydrous material)

Chemistry Review Data Sheet

Chemical structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Levothyroxine sodium	3	Adequate	2-14-05	Reviewed by M Shaikh (Review # 7)
[redacted]	III	[redacted]	[redacted]	3	Adequate	7-22-05	Reviewed by Craig Bertha
[redacted]	III	[redacted]	[redacted]	3	Adequate	5-22-02	Reviewed by Lorenzo Rocca

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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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	Pending		
Pharm/Tox	N/A		
Clinical Pharm	Pending		Sang Chung
LNC	N/A		
Methods Validation	Pending		S. B. Markofsky
DMETS	Pending		
EA	Acceptable	5-2-06	Markofsky (Chem. Rev. #1)
Microbiology	Acceptable	4-12-06	Anastasia Lolas

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

The Executive Summary

The Chemistry Review for NDA 21-924

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA is approvable (AE) pending satisfactory responses to the deficiencies noted in our Discipline Review Letter, and the IR Letter & Filing communication, dated 2-10-06.

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

None (as of the completion of Chemistry Review #1)

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

1) Drug Product

The drug product, which has the proprietary name Tirosint and the established name *levothyroxine sodium soft gelatin 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). The drug product is available in 7 strengths ranging from 12.5 to 150 mcg per capsule. The firm has proposed to package Tirosint 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 [redacted] specification will be used to monitor these capsules.

2) Drug Substance

The drug substance, levothyroxine sodium, USP, is manufactured by [redacted]; and the relevant CMC issues related to the manufacture of this material are described in DMF [redacted]. 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 12.5 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 37.5, 67.5, or 87.5 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 proposed tablet strengths are 12.5; 25, 50, 75, 100, 125 and 150 mcg per capsule. The stability data only support a 9 month expiry (25 ^{0}C with excursions permitted between 15 ^{0}C and 30 ^{0}C) for the capsules packaged in blister packs, but the expiry can be extended with the submission of additional satisfactory longer term stability information.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable (AE) pending the submission of an up-dated and satisfactory post-approval stability protocol, (See Discipline Review Letter) and a satisfactory specification for drug product impurities. A satisfactory Establishment Inspection Report will also be needed before this NDA can be approved.

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

50 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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/s/

Sheldon Markofsky
5/4/2006 03:12:39 PM
CHEMIST

Blair Fraser
5/4/2006 03:53:22 PM
CHEMIST

Initial Quality Assessment

OND Division of Metabolism and Endocrinology Products
NDA: 21-924
Applicant: IBSA Institut Biochimique SA
Stamp Date: 05-DEC-2005
PDUFA Date: 05-OCT-2006
Proposed Proprietary Name: Tirosint T4 Soft Capsule
Established Name: levothyroxine sodium
Dosage form and strength: soft capsule, 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg, and 150 mcg
Route of Administration: oral
Indications: Hypothyroidism and pituitary TSH suppression

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing
Review team recommendation: Single primary reviewer (Chemist S. Markofsky)

Time goals:

- **Initial Quality Assessment in DFS: by 23-DEC-2005**
- **Chemistry filing memo in DFS: by 19-JAN-2006**
- Filing decision "Day 45": 19-JAN-2006 (tentative; to be set by Clinical Division)
- Filing review issues sent to applicant "Day 74": 17-FEB-2006 (tentative; to be set by Clinical Division)
- **Chemistry Review (DR/IR) letter: by 05-MAY-2006**
- Mid-cycle meeting "Month 5": 05-MAY-2006 (tentative; to be set by DMEP)
- **Final Chemistry Review "Month 8": by 05-AUG-2006**
- PDUFA: 05-OCT-2006

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	*Not Applicable*
CDRH	*Not Applicable*
EA	*To be determined by Primary Reviewer*
EES	To be sent by Primary Reviewer
DMETS	Labeling consult request will be sent as part of the Clinical Division's consult request.
Methods Validation	*Validation may be requested of FDA labs.*
Microbiology	*To be determined by Primary Reviewer.* A consult request may be sent for the review of microbiology controls for the drug product.
Pharm/Tox	*To be determined by Primary Reviewer*

Summary:

- Levothyroxine sodium is a narrow therapeutic range drug that has been widely available in the U.S. for over half a century, mostly as unapproved products until recently. In 1997 FDA decided that these products must have approved as 505(b)(2) or 505(j) applications.
- The associated IND is IND 70,039. The NDA is filed as a 505(b)(2) application.
- The drug substance, levothyroxine sodium, has compendial monographs (USP and Ph. Eur.) Reference is made to DMF[redacted] for information on the manufacturing and controls of the drug substance. This DMF was found adequate for a tablet product on 14-FEB-2005 (Chem. Review #7) and there has been no revision since. Both the drug substance and drug product manufacturers implement the USP monograph requirements (acceptance criteria and test methods) for quality control. No further assessment of the drug substance (in DMF and NDA) is necessary.

[redacted]

2 Page(s) Withheld

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Withheld Track Number: Chemistry- 3

Initial Quality Assessment

Supporting NDA or IND:
IND 70,039

Supporting DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
[redacted]	II	[redacted]	levothyroxine sodium	LOA is provided. No chemistry review is needed: The item referenced was found adequate for a tablet product on 14-FEB-2005 and there has been no revision since.
[redacted]	III	[redacted]	[redacted]	LOA is provided. No chemistry review is needed: The item referenced was found adequate for a tablet product on 22-JUL-2005 and there has been no revision since.
[redacted]	II	[redacted]	[redacted]	LOA is provided. The referenced item is in the DMF amendment dated 27-JAN-2005 and may need a chemistry assessment.

Manufacturers:

DRUG SUBSTANCE	DRUG PRODUCT
Manufacturer and tester: Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl, Austria	Manufacturer, tester, and packager: IBSA Manno 1 Centro Insema CH-6928 Manno, Switzerland Microbiology tester: IBSA Microbiological Laboratory Via al Ponte 13 CH-6903 Lugano, Switzerland and Via Cantonale-zona Serta CH-6814 Lamone, Switzerland

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/s/

Suong Tran
12/21/2005 11:58:25 AM
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already discussed with S. Markofsky

Blair Fraser
12/21/2005 12:24:49 PM
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