CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-924

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
NDA 21-924

NAME OF APPLICANT / NDA HOLDER
Institut Biochimique SA (IBSA)

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Tirosint™

ACTIVE INGREDIENT(S)	STRENGTH(S)
Levothyroxine Sodium	12.5, 25, 50, 75, 100, 125, 150 mcg

DOSAGE FORM
Soft Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
Two patent applications submitted but neither issued.		

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☐ Yes	☐ No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Clarence Jones	11/28/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Clarence E. Jones, Ph.D.	
Address: 8602 Mossford Drive	City/State: Huntington Beach, CA
ZIP Code: 92646	Telephone Number: 714-963-0078
FAX Number *(if available)*: 714-964-9270	E-Mail Address *(if available)*

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 3542a (7/03)

PEDIATRIC PAGE

NDA 21-924

Stamp Date: December 5, 2005 **UFGD: October 5, 2006**

HFD-510 **Trade and generic names/dosage form: TIROSINT™ (levothyroxin sodium capsules), 25, 50, 75, 100, 125, and 150 mcg.**

Applicant: Institute Biochimique SA (IBSA) **Therapeutic Class: 3S**

Indications previously approved: None
Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 2

Indication #1:
Hypothyroidism - As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total congenital absence of the thyroid gland, or from the effects of surgery, radiation, or drugs, with or without the presence of goiter.

Indication #2
Pituitary TSH Suppression - In the treatment or prevention of various types of euthyroid goiters (see **WARNINGS** and **PRECAUTIONS**), including thyroid nodules (see **WARNINGS** and **PRECAUTIONS**), subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter (see **WARNINGS** and **PRECAUTIONS**) and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin- dependent well-differentiated thyroid cancer.

Is there a full waiver for this indication (check one)?

☐ ✓ **Yes:**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ ✓**Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other: children/infants may be unable to swallow capsule.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: *Pituitary TSH Suppression* - In the treatment or prevention of various types of euthyroid goiters (see **WARNINGS** and **PRECAUTIONS**), including thyroid nodules (see **WARNINGS** and **PRECAUTIONS**), subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter (see **WARNINGS** and **PRECAUTIONS**) and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin- dependent well-differentiated thyroid cancer.

Is there a full waiver for this indication (check one)?

- ☐ ✓ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ ✓ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: HFD-960/ Grace Carmouze

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

/s/

Jena Weber
10/10/2006 11:21:57 AM

Pediatric Waiver Request

Since Synthroid received a pediatric waiver (7/24/2002 FDA Approval Letter), IBSA requests that consideration be given to granting T4 Soft Capsules a similar exemption from the requirement of performing a clinical trial(s) in a pediatric population. Because T4 Soft Capsules cannot be crushed to facilitate administration to young patients who have difficulty swallowing, it was necessary to modify the class labeling to accommodate this difference as highlighted (in red) in the proposed labeling provided in the Summary, Attachment 3. It is not recommended that T4 Soft Capsules be administered to Newborns for the same reason (also highlighted in red in the proposed labeling).

Samples and Labeling

As per 21 CFR 314.50(e)(1), samples of the drug substance (levothyroxine sodium) and T4 Soft Capsules will be sent to FDA upon request. It is assumed, however, that some of the samples of drug product might actually be obtained from [redacted] since they were required to retain a sufficient number of capsules from each batch of the three dosage strengths evaluated in the BE studies for FDA to complete (at least five times) all testing required for product release (21 CFR 320.38, Retention of Bioavailability Samples). Samples of finished market packaging will also be provided upon request [21 CFR 314.50(e)(1)(ii)].

Three copies of the analytical methods and related descriptive information contained in the CMC section necessary for FDA to perform sample testing and methods validation will be included with the CMC Review Copy of the application (Volumes 2 – 4), while a single copy of the draft labeling [21 CFR 314.50(e)(2)(i)/(ii)] is attached to this section and consists of the product insert and labels that will be affixed to either the aluminum foil of the blister pack or boxes in which the blister packs will be directly placed (***Attachment 5)***. In addition, mock-ups of the blisters, boxes, and capsules will be included.

Case Report Tabulations

Tabulations of the information contained in the case report forms completed for AA05227 and AA05228 [21 CFR 314.50(f)(1)] are provided in the respective reports. Since none of the volunteers died or were discontinued because of an AE, however, actual case report forms are not being included in the application. Should FDA decide it wants to review the CRFs for either study, IBSA will submit them in a format that is acceptable to the agency.

Soft Capsule dissolution study presented in IND 70,039 (Section 7, Attachment 2, page 10), and indicate that each of the three batches of the seven dosage strengths meet the USP requirements for stage I release of active. Please note that a report of the first dissolution study will be attached to the second study report for convenience in reviewing all information relating to the T4 Soft Capsule dissolution profile.

Microbiology

Not applicable.

Clinical/Statistical

As discussed in the Introduction to this NDA Summary, the Sponsor is relying on past FDA findings that an oral levothyroxine sodium product is equally effective to an approved product if bioequivalent, and the excipients in T4 Soft Capsules can be safely administered to humans. Moreover, the limited clinical data generated in the human pharmacokinetic studies described above indicate that a single mega-dose of T4 Soft Capsules (i.e. 600 µg) is as well-tolerated as the approved comparator Synthroid*.

One issue relating to product safety/efficacy that needs to be addressed is that IBSA is requesting market approval for seven T4 Soft Capsule dosage strengths (12.5, 25, 50, 75, 100, 125, 150 µg), the lowest one of which is unavailable in a tablet formulation. It should be noted, however, that FDA has implicitly approved a 12.5 µg dose of each of the tablet formulations (i.e. found them to be safe and effective), as the 25 µg tablet dosage strengths are scored presumably to allow for specific patient populations to either be started at 12.5 µg/day or adjusted in 12.5 µg increments as per class labeling under DOSAGE AND ADMINISTRATION. Furthermore, it could be argued that it would be preferable for a patient to take a 12.5 µg T4 Soft Capsule (which meet the same product release specifications as the other dosage strengths, including inter-capsule variability, dissolution, stability, etc.) as an initial starting dose or for dose adjustment, unless of course the tablet manufacturers have demonstrated to FDA that 25 µg tablets can be cleaved into two essentially identical pieces with the same uncompromised qualitative/ quantitative characteristics as the parent.

Risk-Benefit

It is expected that the risk/benefit for patients taking T4 Soft Capsules would be comparable to the tablet formulations currently being marketed in the U.S. Although no postmarketing studies are currently being considered, an Italian study comparing T4 Soft Capsules to a European tablet formulation will be completed in the near future.

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* Nine subjects experienced an adverse event possibly, probably, or almost certainly-related to treatment in AA05227; two after receiving T4 Soft Capsules (1 heart racing, 1 headache) and seven following Synthroid administration (3 headache, 1 dizziness/nausea, 1 dizziness alone, 1 jittery, 1 vaginal spotting). In AA05228, eight subjects experienced an adverse event possibly, probably, or almost certainly-related to treatment (A = 50µg, B = 100 µg, C= 150 µg): 1 dizziness (A), 1 nausea/lower back pain (A), 1 heart pounding (A), 1 fatigue/muscle ache (A) and palpitations/muscle ache (B), 1 headache (C), 1 headache/lower back pain (C), 1 headache/palpitations (C), and 1 loose stools (C). Please also see the Unithroid Medical Officer (Jean Temeck) 7/21/2000 Review for an excellent summary of the clinical safety and effectiveness of levothyroxine sodium.

DEBARMENT CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, IBSA hereby certifies that:

IBSA did not and will not use in any capacity the services of any person debarred under subsection 306(a) or 306(b) in connection with its 505(b)(2) application for T4 Soft Capsules.

By: _____ Date: 11-18-2005
Printed Name: Giuseppe Mautone
Title: Director R&D IBSA

By: _____ Date: 11/28/05
Printed Name: Clarence Jones, Ph.D.
Title: Consultant to IBSA

DEBARMENT CERTIFICATION [redacted] (hereinafter [redacted], in accordance with the requirements of the Federal Food, Drug and Cosmetic Act, certifies that to the best of its knowledge, its [redacted] is not and will not be using any person debarred under 21 USC section 306 subsection (a) or (b) in any capacity in connection with the performance of this study or studies.

[redacted] also certifies that to the best of its knowledge, [redacted] is not and will not be using any person or affiliate person/firm for whom convictions subject to debarment have occurred in the last five (5) years in any capacity in connection with the performance of this study or studies.

If at any time after execution of this Agreement, [redacted] becomes aware tha[redacted] or any person employed thereby or any affiliate person/firm is in the process of being debarred, [redacted] hereby certifies that they will so notify Sponsor at once.

Gilbert Godin, P.E., M.B.A.
President & CEO

November 19, 2004
Date

S:\PMD\TEMPLATE\Legal\Debarment Certification 2001.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

[redacted]

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Giuseppe Mautone	Director R&D
FIRM / ORGANIZATION: Institut Biochimique (IBSA)	
SIGNATURE	DATE: 11/15/2005

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (2/03)

Norma Jones
Consultant to IBSA 2/28/2006

Weber, Jena M

From: Weber, Jena M
Sent: Friday, October 13, 2006 5:03 PM
To: CDER-APPROVALS
Subject: NDA 21-924

From the Division of Metabolism & Endocrinology Products

NDA 21-924
Tirosint (levothyroxine sodium capsules)
25, 50, 75, 100, 125, and 150 mcg.
Institute Biochimique SA (IBSA)
Approved - Friday October 13, 2006
This new drug application provides for the use of Tirosint as replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, or in the treatment or prevention of various types of euthyroid goiters, as an adjunct to surgery and radioiodine therapy in the management of thyrotripin-dependment well differentiated thyroid cancer.

NDA 21-924 was administratively split; separate action letters issued:

NDA 21-924 AP
NDA 22-121 NA (for 12.5 mcg)

Thanks,
Jena Weber

Project Manager
Division of Metabolism & Endocrinology Products
New e-mail address: Jena.Weber@fda.hhs.gov

4. The distributor named is located in Switzerland (CH). Please provide information on the manufacturer's point of contact in the United States.

5. Revise the usual dosage statement to read "Usual Dosage: See full prescribing information for dosage and administration."

B. BLISTER LABELS

See GENERAL COMMENTS A2 through A5.

C. CARTON LABELING

1. See GENERAL COMMENTS A3, A4, and A5.

2. Delete the green stripe in the lower left hand of the carton, since it increases labeling similarity between product strengths and may increase the potential for product selection errors.

3. Revise "Batch:" and "Expiry date:" to read "Lot:" and "Exp:" respectively.

4. "See full prescribing information..." statement should be revised to read "Usual Dosage: See package insert for dosage information". We refer you to 21 CFR 201.55 for guidance.

D. INSERT LABELING

HOW SUPPLIED

See GENERAL COMMENT A4.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so.

These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber at 301-796-1306.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Mary Parks
10/6/2006 05:35:25 PM

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

11 5pm 10/5/06

plication : NDA 21924/000 Sponsor: INSTITUT BIOCHIMIQUE
Org Code : 510 CH 6915
Priority : 3S PAMBIO NORANCO, , SZ

Stamp Date : 05-DEC-2005 Brand Name : TIROSINT (LEVOTHYROXINE
PDUFA Date : 05-OCT-2006 SODIUM) CAPSULES
Action Goal : Estab. Name:
District Goal: 06-AUG-2006 Generic Name: LEVOTHYROXINE SODIUM CAPSULES
Dosage Form: (CAPSULE)
Strength : 12.5 - 150 MCG/CAPSUL

FDA Contacts:	E. GALLIERS	Project Manager (HFD-510)	301-796-1211
	S. MARKOFSKY	Review Chemist	301-796-1412
	B. FRASER	Team Leader	301-796-1671

Overall Recommendation: ACCEPTABLE on 05-OCT-2006by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
IBSA (INSTITUT BIOCHIMIQUE SA)
MANNO 1 CENTRO INSEMA
MANNO, , SZ CH-6928

DMF No: AADA:

Galliers, Enid M

From: Olagbaju, Bose*
Sent: Thursday, October 05, 2006 4:23 PM
To: Markofsky, Sheldon B; Fraser, Blair; Galliers, Enid M
Subject: FW: Overall OC Recommendation NDA 21924/000

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@CDER.FDA.GOV). To contact the EES technical staff, send an email to CDER EES Help (EESHELP@CDER.FDA.GOV). Thank you.

Weber, Jena M

From: Adams, Shawnte L
Sent: Tuesday, September 26, 2006 8:08 AM
To: Weber, Jena M
Cc: Markofsky, Sheldon B
Subject: RE: OC inspection for NDA 21-924

The last inspection is scheduled to be completed on the 5th of October. We will have our decision in as early as possible on the 5th since we have no inspection history on any of the pending firm's.

Thanks

Shawnte L. Adams
Program Analyst
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-2063 (Fax)

From: Weber, Jena M
Sent: Tuesday, September 26, 2006 7:13 AM
To: Adams, Shawnte L
Cc: Markofsky, Sheldon B
Subject: OC inspection for NDA 21-924
Importance: High

Please let me know when you expect to complete and render a decision on the establishment status for NDA 21-924 (Tirosint). The UFGD is 10/5/06.

Thanks,
Jena

Project Manager
Division of Metabolism & Endocrinology Products
New e-mail address: Jena.Weber@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-924

DISCIPLINE REVIEW LETTER

Institut Biochimique SA (IBSA)
Attention: Clarence E. Jones, Ph.D.
U.S. Agent
8602 Mossford Drive
Huntington Beach, CA 92646

Dear Dr. Jones:

Please refer to your November 30, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TIROSINT™ (T_4 soft capsules), 12.5, 25, 50, 75, 100, 125, and 150 mcg.

Our review of the Chemistry, Manufacturing and Controls section of your submission is in progress. Upon further review, we request that you revise the package insert to reflect the following changes. Please respond in writing to your NDA file.

1. The established name should use "capsules" rather than "soft capsules" in all of the labeling. We suggest that you consider placing the word "capsules" outside of the parenthesis. If this word appears on the inside, you will not be able to use the proprietary name (TIROSINT) for any other dosage form of levothyroxine sodium. In the **DESCRIPTION** section however, you should state that the dosage forms are "soft gelatin capsules."

2. Also, please specify the route of administration of the drug product in the **DESCRIPTION** section.

3. We previously requested that you develop a system for clearly distinguishing the different strengths of TIROSINT. In this regard, please provide appropriate information that identifies the packaging of the various strengths in the **HOW SUPPLIED** section.

4. The name of the company and its place of business should appear at the end of the package insert.

5. Place the established name of the drug (in parentheses), immediately after or under the proprietary name (TIROSINT). The capsule strength should appear under the established name on the cartons and backside of the blister packs.

6. For all labeling, the established name should be in letters that are at least half as large as the proprietary name.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber at 301-796-1306.

Sincerely,

{See appended electronic signature page}

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

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/s/

Mary Parks
9/1/2006 10:14:32 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-924

DISCIPLINE REVIEW LETTER

Rev.

Institut Biochimique SA (IBSA)
Attention: Clarence E. Jones, Ph.D.
U.S. Agent
8602 Mossford Drive
Huntington Beach, CA 92646

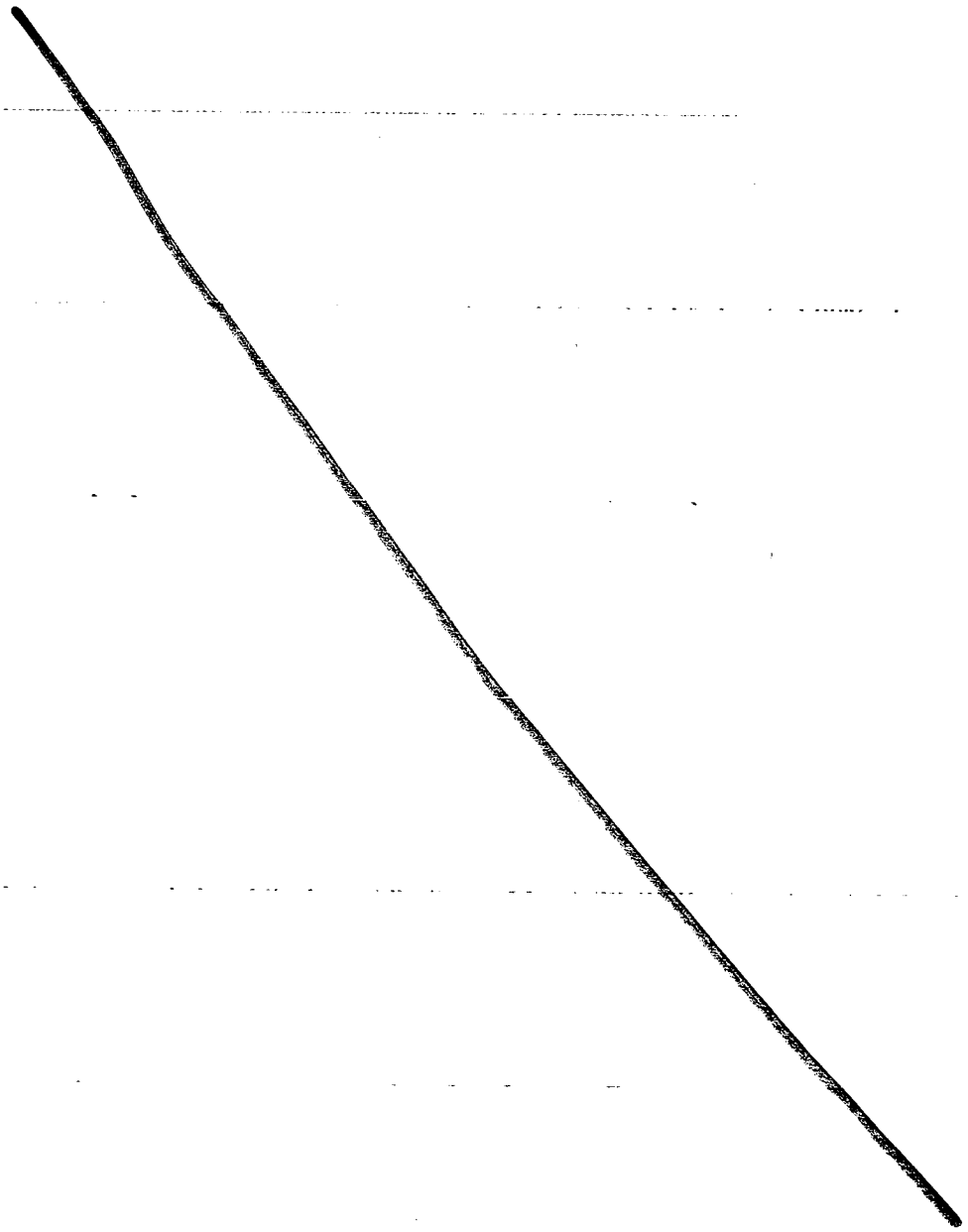
Dear Dr. Jones:

Please refer to your November 30, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tirosint™ (T_4 soft capsules), 12.5, 25, 50, 75, 100, 125, and 150 mcg.

We also refer to your submission dated March 30, 2006, to our filing letter dated February 10, 2006, (requesting additional information), and to our communication dated May 5, 2006. Please note that this correspondence serves to clarify the contents of the May 5, 2006, letter. Revisions appear in bold print.

Our review of the Chemistry, Manufacturing and Controls section of your submission is in progress. Upon further review of your application, we have identified the following deficiencies. Please address these in writing to your NDA file.

5. Submit the protocol you referred to as "the following years," in Attachment 15 of the March 30, 2006, amendment **at least 3-months prior to the action goal date of October 5, 2006.** This protocol should be updated to include the monitoring of Individual Known Impurities, Individual Unknown Impurities, and Total Impurities by validated analytical methods. Additionally, please modify the protocol to include the new T_3-assay-method and the revised dissolution method.



Your assertion would be better supported by actual data that substantiate your claim. Thus, while it is not an Agency requirement to establish a specification for the [redacted] r in the drug product or drug substance, we encourage you to do so.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber at 301-796-1306.

Sincerely,

{See appended electronic signature page}

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

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/s/

Mary Parks
5/18/2006 07:49:26 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Pharmaceutical Sciences
New Drug Microbiology Staff
Bldg 21, Room 3657
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FACSIMILE TRANSMITTAL
From: Anastasia Lolas
Tel: (301) 796-1566
Fax: (301) 796-9737

Message To: Dr. Clarence E. Jones
US Agent for IBSA Institut Biochimique SA
Fax Number: (714) 964-9270
Phone Number: (714) 963-0078

Date: March 2, 2006

This Message Transmitted from: Fax No. 301-796-9737
Number of Pages: 1 including this transmittal sheet

MESSAGE: Request for additional information regarding NDA 21-924

I'm currently reviewing NDA 21-924 and I need additional information in order to complete my review. Please provide a response to the following questions to me via fax (301-796-9737) or e-mail (Anastasia.Lolas@fda.hhs.gov) and submit an amendment to the Division of Metabolism and Endocrinology Products. If you have any questions, please contact me at 301-796-1566.

1. *Please provide a summary of the microbial limits test method validation.*
2. *Please provide the post-approval testing protocol for the microbial limits test. Will each lot of product be tested for microbial limits?*
3. *Please provide the post-approval stability protocol for the microbial limits test.*

Thank you,

Anastasia Lolas
Reviewer, New Drug Microbiology Staff
OPS/CDER/FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-924

Institut Biochimique SA
Attention: Clarence E. Jones, Ph.D.
U.S. Agent
8602 Mossford Drive
Huntington Beach, CA 92646

Dear Dr. Jones:

Please refer to your November 30, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tirosint™ (T4 soft capsules), 25, 50, 75, 100, 125, and 150 mcg.

We also refer to your submissions dated December 13, and 20, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 17, 2006, in accordance with 21 CFR 314.101(a).

However, in our filing review, we have identified the following potential review issues:

Biopharmaceutics/Clinical Pharmacology:

1. Levothyroxine dissolution profiles were not consistent among capsules within the same batch and strength, and thus, the results were not acceptable. Therefore, we recommend that you develop a dissolution method with consistent levothyroxine release from the soft gel capsule. USP Apparatus I (basket) is known to be suitable for soft gel dissolution study. [redacted]
   Please submit justification on your selection of dissolution medium. For example, at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) should be tested. For reference, please consult FDA publication, Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations.

2. A graphical summary of dissolution study results should also be submitted.

General Administrative:

For a foreign sponsor, both the applicant and US agent must sign FDA forms 356h, 3397 (userfee@FDA.GOV), 3454 and 3455 (Financial Disclosure), and 3542a (Patent Information). Please resubmit with all appropriate signatures.

For the Drug Substance:

A specific rotation test for levothyroxine sodium does not accurately account for the amount of [redacted] that may be in your levothyroxine sodium (drug substance). Accordingly, as part of your acceptance testing of the drug substance, please provide a specification for the [redacted] isomer, as for example, by a validated chiral HPLC method.

For the Drug Product:

[redacted]

2. Please provide an executed (signed) batch record for a typical batch of the levothyroxine sodium capsules, prepared by your proposed method of manufacture.

[redacted]

4. Please justify your lack of an in-process-control test to monitor the seal integrity of the capsules after they have been formed.

5. If you propose to perform any reprocessing of your drug products, you should describe the procedures that will be utilized.

6. You should establish release and stability (long term and accelerated) specifications for Individual Known Impurities, Individual Unknown Impurities and Total Impurities, and provide an adequate number of Certificates of Analysis (COAs) to support your proposed specifications. Also, please provide a copy of an HPLC trace taken from the analysis of the most potent and oldest capsules in the stability program. The chromatographic trace should show all detectable impurities and identify all known impurities.

7. Please indicate if the specification for Loss on Drying (LOD) reflects only water loss or other substances that are volatilized as well, and explain the basis of your assertion. If the LOD test does not only reflect water loss, you should establish a release and stability specification for the moisture content of the drug product (as for example by a Karl Fischer titration).

8. A dimensional drawing of your proposed blister pack should be submitted.

9. Your Letter of Authorization (LOA), provided on pp. 196 in Vol. 1.2, references [redacted] for one your blister pack materials. However, according to pp. 181-184 of Vol. 1.2, you intend to use [redacted] Please explain the discrepancy or provide a corrected LOA.

10. Although you have submitted information on your on-going stability tests, you should supply a post-approval stability protocol, as well as post-approval stability commitments. In this regard, you may find help in the Chemistry Guidance section of the FDA/CDER web site under: Submitting Documentation for the Stability of Human Drugs and Biologics.

11. The manufacturing process should be targeted to release capsules with an average assay of 100% of label claim. Accordingly, please explain the consistently high (over 100%) T_4 assay results for your three batches (040704, 040705, and 040706) of the 150 mcg capsules. Similarly, clarify why the average assay for Content Uniformity revealed in the three COAs shown on pp. 245 A, B, & C of Vol. 1.2 of your submission is consistently above 100%.

12. Please specify the Limits of Detection (LOD) and Limits of Quantitation (LOQ) for the T_3 assay in the [redacted] capsules. If these LODs and LOQs are not sufficiently sensitive to accurately determine the [redacted] acceptance criteria at this strength (or any other low strength), you should revise your method.

[redacted]

14. Some patients will need to take two capsules to obtain a daily dose of 37.5, 67.5, or 87.5 mcg, etc. of levothyroxine. If two packages of different strengths are opened for this purpose, there is a possibility of a patient taking two capsules of the same potency, since the appearance of all your capsules is identical, even though the packages are color-coded. The Agency regards this situation as a potential safety hazard. Therefore, you should develop a system for clearly distinguishing the individual capsules of different strengths.

We are providing the above comments to give you preliminary notice of review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of all deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, please call Ms. Jena Weber at 301-796-1306.

Sincerely,

{See appended electronic signature page}

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

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/s/

Mary Parks
2/10/2006 04:30:22 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: David Hussong, NEW DRUG MICROBIOLOGY STAFF OC/OO/CDER/OPS/NDMS HFD-805

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Scott N. Goldie, PhD for Shelly Markofsky, PhD Division of Pre-Marketing Assessment I, Off. of New Drug Quality Assessment

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 1, 2005		21924	New NDA Application	10 January 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TIROSINT T4 Soft Capsules	Standard	Type 1 S (Standard)	1 May 2006

NAME OF FIRM: IBSA Institut Biochimique SA

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☒ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology review requested of New NDA application. Please direct questions to Shelly Markofsky, PhD at 61412. Shelly has the original volumes. Copies will be provided.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
{See appended electronic signature page}	☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Scott Goldie
2/1/2006 09:50:31 AM

Weber, Jena M

From: Chung, Sang
Sent: Tuesday, January 24, 2006 10:18 AM
To: Weber, Jena M
Cc: Markofsky, Sheldon B
Subject: NDA 21-924 (levothyroxine soft gel capsule) filing

Jena,

The followings are comments related to the filing. For the DSI inspection comment, it has been OCPB practice, and let me know if you find any other rules on that. Thanks, Sang

Levothyroxine dissolution profiles were not consistent among capsules in the same batch and strength, and thus the results were not acceptable. Therefore, it is recommended that the sponsor develop a dissolution method with consistent levothyroxine release from the soft gel capsule. USP Apparatus I (basket) is known to be suitable for soft gel dissolution study. [redacted] ustification on the selection of dissolution medium should be submitted. For example, at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) should be tested (refer Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations).

Graphical summary of dissolution study results should be submitted.

In general, DSI inspection for the clinical study and analytical study is recommended for the pivotal BE studies especially in 505(b)(2) application. However, the clinical study and analytical study site were inspected by DSI in 2003-2004 related to Levo-T (NDA 21-342 S-003). Therefore, DSI inspection will not be requested unless there is any other regulatory concern.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
WO22, RM 4447

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/12/06		21-924	Original NDA	11/30/05 8/1/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tirosint	S	Thyroid	**6/1/06**

NAME OF FIRM: IBSA

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Tradename review request; all LBL available via ERD.

PDUFA DATE: **10/5/06**

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jena Weber
1/12/2006 09:49:46 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-924		Supplement Number	
Drug: Tirosint (T4 capsule)		Applicant:IBSA	
RPM: Jena Weber		DMEP	Phone: 301-796-1306

Application Type: ( ) 505(b)(1) (✓) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (✓) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	NA
❖ User Fee Goal Date	**October 5, 2006**
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number No fee submitted
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No

• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	NN
• OC clearance for approval	9/25/06
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(✓) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. **314.53(c)(2)(ii)**	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(✓) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	NO
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	✓

General Information	
❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NDA admin. split; NDA 22-121 for 12.5 mcg strength was NA on 10/13/06.
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	9/14/06
• Original applicant-proposed labeling	11/30/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC – 7/11/06 DMETS – 10/2/06 DSRCS - NN
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	9/14/06
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NO
• Documentation of discussions and/or agreements relating to post-marketing commitments	NN
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA
❖ Advisory Committee Meeting	
• Date of Meeting	NN
• 48-hour alert	NN
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DD 10/6/06
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9/28/06
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	4/12/06
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	NN
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NN
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	10/6/06
❖ Demographic Worksheet *(NME approvals only)*	NN
❖ Statistical review(s) *(indicate date for each review)*	NN
❖ Biopharmaceutical review(s) *(indicate date for each review)*	8/30/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NN
• Bioequivalence studies	NN
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	9.1, 8.31, 5.4.06
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Granted 5/2/06
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	4/12/06
❖ Facilities inspection (provide EER report)	Date completed: 10/5/06 (✓) Acceptable ( ) Withhold recommendation
❖ Methods validation	(✓) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NN
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NN
❖ CAC/ECAC report	NN

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/s/

Jena Weber
10/26/2006 08:50:54 AM