

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-121**

**MEDICAL REVIEW(S)**

## MEDICAL REVIEW OF NDA SUBMISSION

**NDA:** 22-121, NDA 21-924

**DRUG:** Tirosint (levothyroxine sodium), 13 mcg capsules

**INDICATION:** Treatment of hypothyroidism

**COMPANY:** IBSA, Inc.

**DATE OF SUBMISSION:** August 1, 2007

**DATE OF REVIEW:** July 31, 2007

---

Institut Biochimique SA (IBSA) has submitted this complete response to the Approvable action letter dated April 20, 2007 requesting the approval of the 13 mcg dosage strength of Tirosint (levothyroxine sodium) capsules.

In December, 2005 IBSA submitted an NDA seeking approval of Tirosint capsules (multiple doses from 12.5 mcg to 150 mcg) for 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 thyrotropin-dependent well differentiated thyroid cancer. The NDA was administratively unbundled such that Tirosint capsules at doses of 25, 50, 75, 100, 125 and 150 mcg, were approved under NDA 21-924 and Tirosint capsules, 12.5 mcg were Not Approved under NDA 22-121. The deficiencies stated in the Not Approvable letter were as follows:

*There is potential for confusion by pharmacists and patients between the two dosage strengths, 12.5 mcg and 125 mcg that is unlikely to be corrected by different color schemes. The clinical consequence of such a medication error is of particular concern if a patient with underlying cardiac disease is given the higher dose in lieu of the 12.5 mcg dose. Such a medication error has the potential for aggravating cardiac ischemia or precipitating a myocardial infarction.*

*To address this deficiency, if you wish to pursue marketing of a dosage strength less than 25 mcg, the Division recommends selection of a dose that is not distinguished from higher dosage strengths by only the placement of a decimal point. For example, a 13 mcg dosage strength will be acceptable and will not require additional clinical studies for approval.*

In October, 2006 IBSA responded to the Not Approved letter recognizing that the potential for confusion by pharmacists and patients between the two dosage strengths, 12.5 mcg and 125 mcg was unlikely to be corrected by different color schemes. They firmly reiterated the need to have a levothyroxine dosage strength less than 25 mcg and proposed labeling changes that included a change in font size such that the 0.5mcg is smaller than the size of the 12 in the 12.5mcg labeling and different from the 125 mcg labeling. (i.e., 12.5 mcg versus 125 mcg). These changes did not adequately address the concerns and a Not Approved letter was issued on January 8, 2007. The deficiencies stated in the Not Approvable letter were as follows:

*The proposed labeling font size changes are not sufficient to address the concerns outlined in the initial not approvable letter dated October 13, 2006. To address this deficiency, the Division continues to recommend selection of a dose that is not distinguished from higher dosage strengths by only the placement of a decimal point. For*

*example, a 13 mcg dosage strength would be acceptable, and will not require additional clinical studies for approval.*

In February 2007, the Company submitted a complete response to the Not Approved letter proposing a 13 mcg dose instead of the 12.5 mcg dose. During the review cycle, the Agency identified significant concerns regarding assay methods and assay validations for analytical studies conducted at \_\_\_\_\_ site from January 2000 to December 2004. These findings raised questions regarding the validity of results of any study conducted during that period. For this application (NDA 21-924 and NDA 22-121), one of the pivotal bioequivalence trials, Study AA05227, was conducted by MDS. Therefore, an Approvable letter was issued on April 20, 2007, stating:

*Thus, serious questions remain about the validity of bioequivalence data generated by \_\_\_\_\_ in studies during this time period that have not been inspected by FDA, including the study you have submitted in support of your application. Accordingly, with respect to Study AA05227 submitted in your application, we request that you do one of the following, in order of FDA preference:*

- 1. Repeat the bioequivalence studies.*
- 2. Re-assay the samples for levothyroxine at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period.*
- 3. Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of bioequivalence studies and bioanalytical data, and selected by your company rather than by \_\_\_\_\_ to verify the results obtained by \_\_\_\_\_*

Method of \_\_\_\_\_ data validation: In this complete response, IBSA chose to have a scientific audit of the results of Study AA05227 performed by an independent expert, \_\_\_\_\_. The assay validation data, including all raw data, and study result data were reviewed for accuracy, completeness and adherence to regulatory requirements. As outlined in Dr. Sang Chung's review, the independent audit and therefore, the Sponsor's complete response is complete and acceptable.

Label Review: Upon label review with the currently approved label, the Sponsor has made the following changes in the proposed label:

1. WARNINGS: Underlining has been removed from the statement: Levothyroxine sodium should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism.
2. DOSAGE AND ADMINISTRATION, Specific Patient Populations, Newborns: Underlining and All CAPS has been removed from the statement: TIROSINT is not recommended for the treatment of newborns as they may be unable to swallow a capsule.
3. HOW SUPPLIED: The 13 mcg dose strength has been added to the table of available Tirosint strengths.

**COMMENT:** These labeling changes are acceptable.

**Recommendations:** APPROVE the addition of the 13 mcg dose of Tirosint.

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

/s/

-----  
Theresa Kehoe  
8/1/2007 07:53:57 AM  
MEDICAL OFFICER

Mary Parks  
8/1/2007 08:58:51 AM  
MEDICAL OFFICER  
concur w/ recommendations

## MEDICAL REVIEW OF NDA SUBMISSION

**NDA:** 22-121, AC

**DRUG:** Tirosint, 12.5 mcg capsules

**INDICATION:** Treatment of hypothyroidism

**COMPANY:** IBSA, Inc.

**DATE OF SUBMISSION:** October 18, 2006

**DATE OF REVIEW:** January 5, 2007

---

IBSA submitted an NDA seeking approval of Tirosint capsules (multiple doses from 12.5 mcg to 150 mcg) for 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 thyrotropin-dependent well differentiated thyroid cancer. The NDA was administratively unbundled such that Tirosint capsules at doses of 25, 50, 75, 100, 125 and 150 mcg, were approved under NDA 21-924 and Tirosint capsules, 12.5 mcg were Not Approved under NDA 22-121. The deficiencies stated in the Not Approvable letter are as follows:

*There is potential for confusion by pharmacists and patients between the two dosage strengths, 12.5 mcg and 125 mcg that is unlikely to be corrected by different color schemes. The clinical consequence of such a medication error is of particular concern if a patient with underlying cardiac disease is given the higher dose in lieu of the 12.5 mcg dose. Such a medication error has the potential for aggravating cardiac ischemia or precipitating a myocardial infarction.*

*To address this deficiency, if you wish to pursue marketing of a dosage strength less than 25 mcg, the Division recommends selection of a dose that is not distinguished from higher dosage strengths by only the placement of a decimal point. For example, a 13 mcg dosage strength will be acceptable and will not require additional clinical studies for approval.*

In this submission, IBSA responds to the Not Approvable letter. The company firmly recognizes the need to have a levothyroxine dosage strength less than 25 mcg. The company also agrees that there is potential for confusion by pharmacists and patients between the two dosage strengths, 12.5 mcg and 125 mcg that is unlikely to be corrected by different color schemes. They propose labeling changes that include a change in font size such that the 0.5mcg is smaller than the size of the 12 in the 12.5mcg labeling and different from the 125 mcg labeling. (i.e., 12.5 mcg versus 125 mcg).

**Reviewer comment:** The proposed label change is subtle and does not adequately address the concern for confusion.

**Recommendation:** Not Approvable

**Comment for the Sponsor:** The proposed labeling font size changes are not sufficient to address the concerns outlined in the initial Not-Approvable letter dated October 13, 2006.

**To address this deficiency, the Division continues to recommend selection of a dose that is not distinguished from higher dosage strengths by only the placement of a decimal point. For example, a 13 mcg dosage strength will be acceptable and will not require additional clinical studies for approval**

**Appears This Way  
On Original**

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

/s/

-----  
Theresa Kehoe  
1/5/2007 02:17:47 PM  
MEDICAL OFFICER

Mary Parks  
1/6/2007 08:28:53 AM  
MEDICAL OFFICER