CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-121

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-121

Institute 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 new drug application (NDA) dated November 30, 2005, received December 5, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tirosint™ (levothyroxine sodium capsules), 13 mcg.

We acknowledge receipt of your submissions dated February 16 and 26, and March 13 and 29, 2007, and your electronic mail dated April 3, 2007.

The February 16, 2007, submission constituted a complete response to our January 9, 2007, action letter.

We have completed our review of this application, as submitted with labeling (package insert and immediate carton and container labels dated March 29, 2007), and it is **approvable**. Before the application may be approved, however, it will be necessary for you to address the bioanalytical analysis that was conducted ——— site for Study AA05227.

FDA has conducted several comprehensive inspections of bioequivalence studies conducted —— since 2000. The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing.

As a result of these findings, —— agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the —— audit during its most recent inspection. 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 [redacted], to verify the results obtained [redacted].

In addition, because one of the Agency's significant findings for the inspected [redacted] studies was the presence of anomalous results, we are requesting for all of the above options that the blood/plasma level results obtained in the study be compared to any published literature or other relevant information that is publicly available.

If you choose to conduct an audit, we request that the completed audit reports be maintained at your site. If the audit finds the study acceptable, we request that you submit a certification to your application that formally attests in writing to the validity of the results obtained [redacted] upon which your application relies. If the audit finds the study to be unacceptable, you should either repeat the bioequivalence study and submit the information within 6 months of the completed audit or withdraw the application. Please note that these audits would also be subject to validity assessment by the Agency upon submission.

The audit criteria provided below includes, but is not limited to, examples of areas that should be evaluated.

- The audit criteria for reviewing pre-study validation data should address whether accuracy and stability were demonstrated with appropriate validation experiments and documentation, and under the conditions of sample processing used for the analysis of samples from study subjects.

- The audit criteria for reviewing the results of the bioequivalence studies should address whether anomalous results were investigated and issues related to contamination were identified and corrected. It should also determine if a comparison of all available original and repeat results demonstrated assay reproducibility, and whether analytical runs were accepted in accordance with established procedures and without bias.

The new bioequivalence data or the re-analysis of the existing data should be submitted to your application as an amendment. If the new information does not support a finding of bioavailability/bioequivalence, the FDA may refuse to approve your application.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Ms. Jena Weber, Project Manager, 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
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