CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-116

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-116

Lloyd Inc.
Attention: W.E. Lloyd, D.V.M., Ph.D.
Chief Executive Officer
P. O. Box 130
604 West Thomas Avenue
Shenandoah, Iowa 51601-0130

Dear Dr. Lloyd:

Please refer to your new drug application (NDA) dated August 19, 1999, received August 20, 1999, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Thyro-Tabs® (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg strengths.

We acknowledge receipt of your submissions dated June 27, July 6 and 31, and August 11, 2000, April 17, May 17 and 23, June 8, July 24, October 5 and 30, and December 14, 2001, and April 22, May 27, September 5 and 25, and October 4, 14, 16, 21, and 22, 2002. We also refer to the telephone conversations between you and Ms. Enid Galliers of this Division on October 22 and 23, 2002, in which you agreed to the editorial changes described below to the labeling.

The April 22, 2002, submission constituted a complete response to the Agency's June 20, 2000, action letter.

This new drug application provides for the use of Thyro-Tabs (levothyroxine sodium tablets, USP) for hypothyroidism and suppression of thyroid-stimulating hormone.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text (package insert enclosed) which includes the following agreed upon revisions:

To the package insert (PI) submitted October 14, 2002:

1. Move the "**R_x only**" statement from the last page (following the **STORAGE CONDITIONS** section) to the top of the package insert so it immediately follows the proprietary and established names and precedes the **DESCRIPTION** section.

2. Replace the current **STORAGE CONDITIONS** statement with "**Store at 25 °C (77°F) with excursions permitted to 15°-30°C (59°-86°F). Protect from moisture and light.**"

3. In the **HOW SUPPLIED** section, delete the column titled (**b)----------(b)-----**

4. Insert the title **"DESCRIPTION"** at the beginning of that section as in the package insert submitted on May 27, 2002.

To the Bottle and Shipper Labels (bottles of 100 and 1000; cartons of 12 bottles (100-ct and 1000-ct) submitted May 27, 2002:

5. Replace the(b)----------(b)---------- with "**R_x only.**"

6. On the side panel of the bottle and shipper labels, replace the phrase (b)----------(b)----------. . ." with the phrase " **Store at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F), protect from moisture and light.**"

Final printed labeling (FPL) must be identical, and include the revisions listed above, to the submitted labeling (text for the package insert submitted October 14, 2002, and bottle and shipper labels submitted May 27, 2002). These revisions are terms of the NDA approval. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-116." Approval of this submission by FDA is not required before the labeling is used.

The Office Clinical Pharmacology and Biopharmaceutics has reviewed the data submitted on October 4, 2002, regarding your dissolution and tolerance specifications for Thyro-Tab tablets and has set the following specifications:

Apparatus Type	USP # 2 (paddles)
Media	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume	500 mL
Speed of Rotation	50 RPM
Tolerance Specifications	N(b)-------(Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes.

In addition, we request that you submit four copies of the introductory promotional materials you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug
Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE

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

/s/

David Orloff
10/24/02 11:38:28 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-116

APPROVABLE LETTER(S)

06.20.00 AE

NDA 21-116

Lloyd Incorporated
Attention: W. E. LLoyd, D.V.M., Ph.D.
Chief Executive Officer
P.O. Box 130
604 West Thomas Avenue
Shenandoah, Iowa 51601-0130

Dear Dr. Lloyd:

Please refer to your new drug application (NDA) dated August 19, 1999, received August 20, 1999, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Thyro-Tabs® (levothyroxine sodium tablets).

We acknowledge receipt of your submissions dated September 22 and December 30, 1999, and January 12, 25, and 29, February 3, March 8, and April 5 and 20, 2000.

We have completed our review of this application, as amended, and it is approvable. The 100 mcg, 175 mcg, 200 mcg, and 300 mcg tablets meet the requirements for stability, bioavailability, and dissolution. However, the 25 mcg, 50 mcg, 75 mg, and 150 mcg tablets fail to meet these requirements. Before this application may be approved, a lower dosage strength (i.e., 25 mcg) must meet the aforementioned requirements to allow for adequate labeling for the safe and effective use of your product. The available dosage strengths of a levothyroxine product must permit initiation of therapy at doses as low as 12.5 mcg daily and must permit titration of the daily dose in increments of 12.5 or 25 mcg. In order to meet this requirement, at a minimum, a 25 mcg dosage strength is required in addition to those strengths noted above that are approvable.

The following deficiencies must be adequately addressed before this application may be approved:

1. **CHEMISTRY, MANUFACTURING AND CONTROLS**

   a. The stability data that were provided for the 25 mcg tablets (pilot batch KA25998 and validation batches KA34198, KA36298, and KA36398) cannot be used to support the three tablet strengths (25, 50, and 75 mcg tablets) representing the lower third of the stability bracket. The data are inconsistent across the four lots. Two out of four lots failed long-term stability within (KA36298 and KA36398), while the other two lots (KA25998 and KA34198) were stable for approximately Submit acceptable accelerated long-term stability data for a minimum of three lots of 25 mcg tablets. The new production, full-scale lots of 25 mcg tablets must be retested under the same storage conditions as the lots previously submitted to the NDA, and

satisfactory results for these three lots must be submitted to support the lower end of the stability bracket. In addition, the 25 mcg tablets may be tested for stability under refrigerated storage conditions (2-8°C) if the current formulation is found to be unstable at 25°C.

b.

c. Provide updated stability data (when available) for those strengths of the drug product for which — of acceptable (25°C) stability have been documented and the data submitted. The issue of shelf-life extension via annual reports will be addressed upon final approval of your NDA.

d. The minimum number of batches required for the post-approval stability commitment is three batches each of the highest and lowest strengths within the stability bracket.

e. Identify any degradants exceeding 1.0 % (relative to the —

f. Since your drug is proposed to be labeled as being a USP-grade product, the non-USP HPLC method utilized for assay and dissolution may only be used as an alternate test. Revise your proposed tests and specifications for the finished drug product to include the USP HPLC test as the regulatory method and your non-USP test as an alternate method.

2. BIOPHARMACEUTICS

a. Based on the data submitted, Thyro-Tabs failed to meet the dissolution tolerance specified in the current USP 24 monograph. Therefore, inclusion of the "USP" designation in the labeling for this product, as you have proposed, would not be allowed.

b. The dissolution curves for the 25 mcg, 125 mcg, and 150 mcg tablets generated using the USP 24 dissolution method do not show adequate similarity to support granting a biowaiver for these tablet strengths based on f_2 calculations. The test/reference criteria for the f_2 calculations were determined as follows: the 300 mcg tablets served as the reference for the 200 mcg, 175 mcg, 150 mcg, and 125 mcg tablets; the 100 mcg tablets served as the reference for the 75 mcg tablets; and the 50 mcg tablets served as the reference for the 25 mcg tablets.

c. The proposed dissolution tolerance — (Q) at —, is not an acceptable quality control measure based on the data submitted. We recommend — (Q) at —

In order to resolve the deficiencies listed in points b. and c. above, we suggest that you either:

1. Develop a new dissolution method that better characterizes your product (e.g., increase paddle speed to — RPM), and generate and submit multi-point dissolution data using this new method for at least three batches of each proposed to-be-marketed tablet strength, or;
2. Generate and submit additional multi-point dissolution data, using the USP 24 method and our proposed tolerances, for at least three batches each of the 25 mcg, 125 mcg, and 150 mcg tablets.

We strongly recommend that you pursue option #1 and also strongly recommend that you consult with the Division of Metabolic and Endocrine Drug Products before conducting additional dissolution studies on your product.

3. LABELING

Labeling comments are deferred pending adequate resolution of the deficiencies listed above.

While not required prior to approval, we are providing the following additional recommendation and request that you address this in your resubmission:

We recommend that stability testing should be initiated for three lots of the 50 mcg tablets to cover the lower end of the stability bracket, in case the 25 mcg tablets should repeatedly fail long-term stability testing and have to be reformulated or subjected to alternate storage conditions (e.g., refrigerated conditions).

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and
Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Archival NDA 21-116
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/DOrloff/JTemeck/Rsteigerwalt/JElHage
HFD-870/HAhn/SJohnson
HFD-820/DWu/DLewis
HFD-002/Jenkins/LRipper
HFD-002/ORM
HFD-102/ADRA
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

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