

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-292

APPROVAL LETTER



Food and Drug
Administration
Rockville MD 20857

NDA 21-292

Genpharm, Inc.
Attention: Eugene M. Pfeifer
U.S. Agent for Genpharm, Inc.
King and Spalding
1730 Pennsylvania Ave., NW
Washington, DC 20006-4706

Dear Mr. Pfeifer:

Please refer to your new drug application (NDA) dated June 27, 2000, received July 6, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Novothyrox (levothyroxine sodium tablets, USP), 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg

We acknowledge receipt of your submissions dated May 11, July 17, and November 9 and 29, 2001; and February 25, March 13, and May 27, 2002. Your submission of November 29, 2001, constituted a complete response to our May 4, 2001, action letter.

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

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted May 27, 2002, [enclosed], and blister, bottle, and carton labels submitted May 27, 2002.) Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-292." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and 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, Maryland 20857

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed your data and has set the dissolution method and tolerance specifications as follows:

| Revised Genpharm Dissolution Method- Levothyroxine sodium | | |
|---|---------------------------|---------------------------|
| | 25 mcg - 175 mcg | 200 mcg - 300 mcg |
| Media | | |
| Volume | | |
| Apparatus | USP apparatus 2 (paddles) | USP apparatus 2 (paddles) |
| Speed | | |
| Tolerance | | |

We note that your data support a 24 month expiry for all presentations and all strengths of this product.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

ENCLOSURE

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-292

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

04-MAY-2001

NDA 21-292

Genpharm Incorporated
Attention: Eugene M. Pfeifer
US Agent for Genpharm Incorporated
King and Spalding
1730 Pennsylvania Ave., NW
Washington D.C. 20006

Dear Mr. Pfeifer:

Please refer to your new drug application (NDA) dated June 27, 2000, received July 6, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for _____ (levothyroxine sodium tablets, USP), 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300 µgm strengths.

We acknowledge receipt of your submissions dated August 9, November 9, and December 8, 2000, February 20, March 15, 16, 27, and 28, and April 10, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CHEMISTRY:

1. Regarding the drug substance, DMF _____, containing chemistry, manufacturing and controls information for levothyroxine sodium, USP, has been found inadequate to support your NDA. A list of deficiencies was forwarded to the DMF holder, _____, in a letter dated December 14, 2000. A satisfactory response to those deficiencies will be needed before the NDA can be approved.
2. Regarding the gelatin used in the formulation for the drug product, please provide information to certify that its source and manufacturing process meet the conditions specified in the 1997 "Guidance for Industry: The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use."
3. Due to the existence of an overage in all pilot-scale batches at release, stability data generated from these batches cannot be used for assessment of product stability and assignment of expiration dating. Stability data derived from the production-scale batches described in the amendment dated March 16, 2001, should be provided. A minimum of 6

months of long-term (25°C/60 % RH) and intermediate (30°C/60 % RH) stability data should be submitted for the following validation lots:

- a. 25-mcg tablets, Lots 25068, 25069, and 25070
 - b. 300-mcg tablets, Lots 25079, 25081, and 25134
 - c. Intermediate-strength tablets, two out of the following four lots: (25076, 25082, 25077, and 25078)
4. Regarding the finished drug product specifications, the identity test should be changed, in order to correspond with the identity test included in the current USP monograph (thin layer chromatography, USP 24, p. 969).

NOMENCLATURE:

The proposed names _____ are not acceptable proprietary names. Please submit a new proprietary name for review.

LABELING:

In addition, it will be necessary for you to submit revised draft labeling. We have enclosed a template label for levothyroxine sodium tablets that has been developed by the Agency, which incorporates revisions to the package insert labeling. Your draft labeling should include product-specific information using the template as a guide. For example, you should amend the third sentence of the "Absorption" section of the "Pharmacokinetics" subsection of the CLINICAL PHARMACOLOGY section of the labeling as follows: "The relative bioavailability of TRADENAME Tablets, compared to an equivalent dose of oral levothyroxine sodium solution, is approximately 99%."

We also have the following additional comments:

CHEMISTRY, MANUFACTURING, AND CONTROLS

1. The combination of the trade name and the established name printed on labels and in all sections of the package insert should be revised to read "TRADEMARK (Levothyroxine Sodium Tablets, USP)."
2. The bold line separating the proprietary name and the established name on the cartons and bottle labels should be deleted or moved below the established name.
3. Your amendment dated March 28, 2001, added a new package size, i.e., a 100-count, cc HDPE bottle. This type of change must be submitted in a supplement after the application is approved or in an original NDA. Therefore, this amendment will not be reviewed with your response to the deficiencies delineated in this letter. However, we note that the following information will be required in your application for the new container:

- a. Letters of Authorization allowing reference to the Type III packaging DMFs for
both bottles and caps as well as _____ for fabrication of
CR caps. used in fabrication of the
- b. Updated stability data for the drug product packaged in the new 100-count bottles
(ICH conditions of long-term and intermediate storage).

BIOPHARMACEUTICS

The dissolution specification for your levothyroxine sodium tablets should be as follows:

Media: _____
Volume: _____
Apparatus: USP apparatus 2 (paddles)
Speed: _____
Units tested: _____
Tolerances: _____

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 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,

{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

Number of Pages
Redacted 13



Draft Labeling
(not releasable)

**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
5/4/01 10:32:35 AM

**APPEARS THIS WAY
ON ORIGINAL**