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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-402

Approval Letter



Food and Drug
Administration
Rockville MD 20857

NDA 21-402

Abbott Laboratories
Attention: Ernesto J. Rivera, Pharm.D.
Regulatory Affairs Project Manager
200 Abbott Park Road
D-491/AP30-1E
Abbott Park, IL 60064-6157

Dear Dr. Rivera:

Please refer to your new drug application (NDA) dated July 31, 2001, received August 1, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Synthroid (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 September 12 and November 20, 2001, and January 29, March 15 and 22, April 15, May 3, 23, 24, and 31, June 6 and 27, and July 11, 12, and 19, 2002.

This new drug application provides for the use of Synthroid (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 and with the minor editorial revisions listed below. Accordingly, the application is approved effective on the date of this letter.

- No change to package insert submitted July 11, 2002.
- No change to hospital unit dose label (blisters of 10 tablets) submitted July 31, 2001.
- No change to professional sample carton and blister cards submitted April 15, 2002.
- The 100-count bottle labels, 1000-count bottle labels, and hospital unit dose cartons (100 tablets) submitted July 31, 2001, are modified as described in your July 11, 2002, submission to add the following two statements:

“Tablet identification change adopted <<month>> 2002.”

“Each tablet contains XXX mcg (X.XXX mg) levothyroxine sodium.”

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted July 11, 2002, professional sample cartons and blister cards submitted April 15, 2002, 100-count stock bottle labels, 1000-count stock bottle labels, and hospital unit dose cartons and blister labels submitted July 31, 2001). 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 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 21-402." Approval of this submission by FDA is not required before the labeling is used.

We suggest that you modify the labeling at a subsequent printing as follows:

(4)

We remind you of your postmarketing study commitment in your submission dated May 24, 2002. The commitment is listed below.

Commitment/Study Description:

To develop an analytical method for the determination of impurities and degradation products in the drug substance and the drug product. The regulatory specifications (drug substance and drug product, release and shelf life) will be revised by adding a test for degradants and/or impurities and setting appropriate acceptance criteria (specified, unspecified, and total impurities).

Commitment Category: CMC –Chemistry, Manufacturing, and Controls

Final Report Submission: by July 31, 2003.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients

entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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 at the following:

Apparatus Type	2 (paddles)
Media	(b)(4)
Volume	500 mL
Apparatus	USP apparatus 2 (paddles)
Speed	50 RPM
Tolerance	(b)(4) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes

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

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**

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this page is the manifestation of the electronic signature.**

/s/

David Orloff

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