CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-292

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-292

Novothyrox (levothyroxine sodium tablet, USP)

Genpharm, Inc.

David B. Lewis, Ph.D.

Division of Metabolic and Endocrine Drug Products
(DMEDP, HFD-510)

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 21-292

2. REVIEW #: 2

3. REVIEW DATE: 26/04/02

4. REVIEWER: David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
ORIGINAL NDA	06/07/00
AMENDMENT	08/12/00
AMENDMENT	20/02/01
AMENDMENT	16/03/01
AMENDMENT	27/03/01
AMENDMENT	28/03/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
AMENDMENT	29/11/01
AMENDMENT	26/02/02
AMENDMENT	15/03/02

- The amendment dated January 29th, 2001 provides responses to the CMC-related deficiencies from the AE letter along with updated stability data (validation lots) and revised draft labeling (package insert and container and/or carton labels).
- The amendment dated February 26th, 2002 provides more updated stability data for the validation lots.
- The amendment dated March 15th, 2002 provides updated (24 months) stability data for the primary stability lots (original submission).

7. NAME & ADDRESS OF APPLICANT:

Name:	Genpharm, Inc.
Address:	85 Advance Road, Etobicoke, Ontario, CANADA M8Z 2S9
Representative:	Dr. Bonnie Southorn, Director CTD & Submissions
Telephone:	(416) 236-2631 (Phone); (416) 236-2940 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Novothyrox
b) Non-Proprietary Name (USAN): levothyroxine sodium tablet, USP
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2); Listed Drug: Unithroid® (levothyroxine sodium tablet, USP), manufactured by Jerome Stevens Pharmaceuticals, Bohemia, NY (NDA 21-210)

10. PHARMACOL. CATEGORY: Thyroid

11. DOSAGE FORM: Immediate-release solid oral tablets

12. STRENGTH/POTENCY: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg per tablet.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

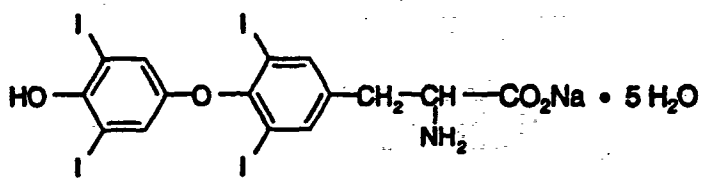
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- Established name (USAN/INN): **Levothyroxine sodium**
- Inverted IUPAC Name: **L-Tyrosine, *O*-(4-hydroxy-3,5-diiodophenyl)-3',5'-diiodo-, monosodium salt, hydrate.**
- Molecular formula: **$C_{15}H_{10}L_4NNaO_4 \cdot 5H_2O$**
- Molecular weight(s): **888.96 g/mol (pentahydrate) and 798.86 g/mol (anhydrous material).**
- The chemical structure is as follows:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
			Levothyroxine sodium	1	Adequate	10/04/02	
				3	Adequate	02/04/01	CMC review No. 1
				3	Adequate	23/04/98	
				3	Adequate	09/08/99	

[redacted]	3	Adequate	16/12/98	
[redacted]	3	Adequate	24/01/97	
[redacted]	3	Adequate	15/11/96	
	3	Adequate	12/02/01	
[redacted]	3	Adequate	07/11/94	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	03/05/01	M. Egas
Pharm/Tox	Acceptable	27/09/00	K. Davis-Bruno, Ph.D.
Biopharm	Acceptable	25/04/01	S. Johnson
LNC			
Methods Validation			
ODS	Acceptable	29/03/02	J. Fan, Pharm. D.
EA	Adequate (CMC Review No. 1)	20/04/01	D. Lewis, Ph.D.
Microbiology			

The Chemistry Review for NDA 21-292

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from the standpoint of chemistry, manufacturing and controls (CMC) information.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

This review addresses the chemistry, manufacturing and controls (CMC) information provided in response to an approvable (AE) letter communicated to the sponsor following the first review cycle. The original NDA was submitted to the Agency on July 6th, 2000 and the CMC review, dated April 16th, 2001 resulted in a recommendation of "approvable" (AE) from the standpoint of chemistry. A letter of deficiencies and requests for information was submitted to the sponsor on May 8th, 2001, to which a response was submitted in the form of a major amendment dated November 29th, 2001. The AE letter included four CMC-related items along with a request to revise the nomenclature and labeling for the drug product. One of the CMC-related items involved a referenced DMF, which was reviewed in support of the original NDA and found to be not adequate for the drug substance; this DMF was subsequently amended by the DMF holder, reviewed, and found adequate to support this NDA (DMF —— , CMC review dated February 4th, 2002, D. Lewis, Ph.D., reviewer).

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product was initially named —— (levothyroxine sodium tablets); the proposed proprietary name was rejected by OPDRA (now Office of Drug Safety, OPS) and by the Division. *The revised proprietary name for the drug product is Novothyrox, which was found acceptable by ODS.* The drug product is an immediate-release solid oral tablet, which is packaged in 5000-count plastic bottles and in unit-dose blister strips. The drug product is manufactured in twelve strengths, ranging from 25 mcg to 300 mcg per tablet. The manufacturer of the drug product is Merck KGaA (Darmstadt, Germany), and the NDA sponsor is Genpharm, Inc. (Ontario, Canada). The drug product formulation includes the following excipients: lactose, corn starch, gelatin, croscarmellose sodium, and magnesium stearate. There are no colorants in the drug product; all tablet strengths are

white, and are distinguished via debossing (numerical statement of strength on each tablet). The manufacturing process involves [redacted] The NDA product represents a revised formulation from that, which has been marketed in Europe, in that the manufacturing excess of levothyroxine sodium has been reduced, in order to target 100 % labeled claim at release. The original stability lots (pilot scale) were released with an overage and the resubmission (amendments covered in this review) addresses comparative stability data for the validation lots (commercial scale), which were released at 100 % of labeled claim and the primary stability lots.

B. Description of How the Drug Product is Intended to be Used

The drug product is proposed for marketing in twelve strengths: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg per tablet. The proposed commercial package presentations are 5000-count HDPE plastic bottles and unit-dose blister packs. Usual dosing for levothyroxine sodium tablets is once daily, with a typical daily dose ranging from 12.5 to 200 mcg per day. The proposed expiry for the drug product is 24 months with storage at controlled room temperature (see USP 24; ca. 25°C). Stability studies conducted under ICH conditions of long-term and intermediate storage (25°C/60 % RH and 30°C/60 % RH, respectively) support this proposed expiry (including permissible excursions 15° to 30°C).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval from the standpoint of chemistry.

III. Administrative

A. Reviewer's Signature

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

15 pages

VII. ESTABLISHMENT INSPECTION

Acceptable, dated May 3rd, 2001 (Requested during the 1st Review Cycle). The EER Summary Report is attached at the end of this review.

29-MAR-2002 FDA CDER EES Page 1 of

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21292/000 Priority: SS Org Code: 510
Stamp: 06-JUL-2000 Regulatory Due: 03-JUN-2002 Action Goal: District Goal: 07-MAR-2001
Applicant: GENPHARM INC Brand Name: [redacted] (LEVOTHYROXINE SODIUM)
NO CITY, , XX Established Name:
Generic Name: LEVOTHYROXINE SODIUM
Dosage Form: TAB (TABLET)
Strength: 25 - 300 MCG

FDA Contacts: S. MCCORT (HFD-510) 301-827-6415 , Project Manager
D. LEWIS (HFD-510) 301-827-6420 , Review Chemist
D. WU (HFD-510) 301-827-6375 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-MAY-2001 by EGASM

Establishment: 9610140 DMF No:
MERCK KGAA AADA No:
DARMSTADT, , GM

Profile: TCM OAI Status: NONE Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted] DMF No: [redacted]
AADA No:
[redacted]

Profile: CSN OAI Status: NONE Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 [redacted] A for fabrication of both bottles and caps as well as [redacted] s used in fabrication of the CR caps.

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: [redacted]
Volume: [redacted]
Apparatus: [redacted]
Speed: [redacted]
Units tested: [redacted]
Tolerances: [redacted]

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

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

/s/

David Lewis
4/26/02 02:04:18 PM
CHEMIST
The application may be approved from the standpoint of chemistry.
no further changes

Sheldon Markofsky
4/29/02 09:53:33 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-292 **DATE REVIEWED:** 04-23-01

REVIEW #: 1 **REVIEWER:** David B. Lewis, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	07-06-00	07-07-00	07-19-00
AMENDMENT	12-08-00	12-11-00	
AMENDMENT	02-20-01	02-22-01	
AMENDMENT	03-16-01	03-22-01	
AMENDMENT	03-27-01	03-28-01	
AMENDMENT	03-28-01	03-28-01	

NAME & ADDRESS OF APPLICANT:

Genpharm, Inc.
85 Advance Road
Etobicoke, Ontario
M8Z 2S9 CANADA
(416) 236-2631 (Phone)
(416) 236-2940 (FAX)

AUTHORIZED US AGENT:

Mr. Eugene M. Pfeifer
King & Spalding
1730 Pennsylvania Ave., NW
Washington, DC 20006
(202) 626-2909 (Phone)
(202) 626-3737 (FAX)

DRUG PRODUCT NAME

Proprietary: _____, Tablets
Established: Levothyroxine Sodium Tablets, USP
Code Name/#:
Chem.Type/Ther.Class: 5S

PHARMACOL. CATEGORY/INDICATION: Treatment of hypothyroidism, thyroid goiter, and thyroid cancer.

SPOTS: _X_ YES ___ NO

Gelatin included in formulation

DOSAGE FORM: Solid Oral tablets

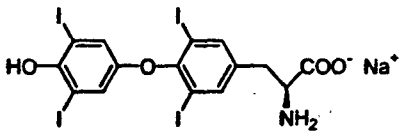
STRENGTHS: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Levothyroxine Sodium, USP $C_{15}H_{10}NI_4O_4Na \bullet xH_2O$ 798 g/mol



SUPPORTING DOCUMENTS: Letters of Authorization, allowing reference to the following DMF's: . IND 59,041 (Levothyroxine Sodium Tablets, USP; Genpharm).

RELATED DOCUMENTS (if applicable): (Type I and Type III DMF's only)

Type/Number	Subject	Holder	Status	Review Date	Letter Date
	Levothyroxine sodium		Not adequate	10-20-00	12-13-00
			Adequate	4-02-01	N/A
			pending	---	N/A
D T			Adequate	4-23-98	N/A
I			Adequate	8-09-99	N/A
			Adequate	12-16-98	N/A
1			Adequate	1-24-97	N/A
			Adequate	11-15-96	N/A
			Adequate	2-12-01	N/A
			Adequate	11-07-94	N/A

CONSULTS: OPDRA

REMARKS: Genpharm, Inc. (Etobicoke, ONT, CANADA) has filed NDA 21-292 in response to the Federal Register Notice of August 14th, 1997 (Volume 62, Number 157), in which drug products

containing levothyroxine sodium were re-classified as new drugs, and were subject to formal NDA application and FDA review. The manufacturer of the *active ingredient* (levothyroxine sodium, USP, T_4) i[illegible]) and the manufacturer of the *drug product* is *Merck KgaA* (Darmstadt, Germany). Since 1972, Merck KgaA has been marketing levothyroxine sodium tablets of an old formulation under the brand name [illegible] throughout Europe, South America, Central America, and Africa. The tablet formulation provided in this NDA was approved in Switzerland, France, and Germany in 1999. This formulation contains a small [illegible] intended for the tablets to be released at [illegible] label claim [illegible]

The amendment dated 12-08-00 provides updated (9-month) stability information. The amendment dated 2-20-01 provides information, regarding the manufacturing overage utilized for the drug product. The amendment dated 3-16-01 provides COA's for several validation batches listed in the 2-20-01 amendment, along with a stability proposal for those batches. The amendment dated 3-27-01 provides updated stability data, statistical analysis of the assay regression, and information, regarding the aluminum foil for use in fabricating the blister packs. The amendment dated 3-28-01 provides for a new container for the drug product (100-count bottles).

CMC information, regarding the drug substance (T_4) is contained in DMF— This DMF has been reviewed and found inadequate to support an NDA. The deficiencies have been forwarded to the DMF holder in a letter dated 12/13/00 and the response is still pending. *The CMC information for the drug product is not satisfactory due to inadequate stability data and other deficiencies.* The stability data provided in this NDA (12 months) was derived from eight pilot-scale lots (3 apiece for the 25 and 300-mcg tablets, and one apiece for the 50 and 100-mcg tablets). Although an excellent stability profile was observed for these pilot-scale lots, they are not acceptable as primary stability lots due to the existence of a small overage at release, which the applicant attributed to variability inherent in the manufacturing process. A second set of stability data is currently being generated from additional production-scale lots that contain no overage at release. The assignment of expiration dating will be based on the results from these lots. The amendment dated 3-28-01 was received within two months of User Fee Date, and, therefore, will not be reviewed. A consult for nomenclature and labeling has been forwarded to OPDRA and the proposed proprietary name [illegible] was not recommended for approval. The results of the cGMP inspections (Merck KgaA and [illegible]) are still pending.

CONCLUSIONS & RECOMMENDATIONS: From a chemistry standpoint, the NDA is approvable, pending satisfactory responses to deficiencies delineated in the reviews of this NDA and DMF— See Draft Letter of deficiencies and information requests to be forwarded to the sponsor.

cc:
Org.
HFD-510/Division File
HFD-820/Chemist/D. Lewis/DG Wu
HFD-510/S. McCort

David B. Lewis, Ph.D.
Review Chemist

R/D Init by:

Filename: NDA 21-292 Revised Review (4-23-01)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

37 pages

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21292/000 Priority: 5S Org Code: 510
Stamp: 06-JUL-2000 Regulatory Due: 06-MAY-2001 Action Goal: District Goal: 07-MAR-2001
Applicant: GENPHARM INC Brand Name: [redacted] (LEVOTHYROXINE SODIUM) [redacted]

NO CITY, , XX

Established Name:
Generic Name: LEVOTHYROXINE SODIUM
Dosage Form: TAB (TABLET)
Strength: 25 - 300 MCG

FDA Contacts:			
	S. MCCORT	(HFD-510)	301-827-6415 , Project Manager
	D. LEWIS	(HFD-510)	301-827-6420 , Review Chemist
	D. WU	(HFD-510)	301-827-6375 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-MAY-2001 by M. GARCIA (HFD-322) 301-594-0095

Establishment: 9610140
MERCK KGAA

DARMSTADT, , GM

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]