CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-292

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

GENPHARM

PATENT INFORMATION

In the opinion and to the best knowledge of Genpharm Pharmaceuticals Inc. there are no relevant patents that claim the drug or the drug products or that claims a method of using the drug product as per CFR 25 § 314.53. See Patent Certification.

Tirtho Uppal
Director, Regulatory Affairs

June 30/2000
Date

APPEARS THIS WAY
ON ORIGINAL

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GENPHARM

PATENT CERTIFICATION

In the opinion and to the best knowledge of Genpharm Pharmaceuticals Inc. there are no relevant patents that claim the drug or the drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drugs or drugs as per CFR 25 § 314.50 (i)(1)(ii).

Tirtho Uppal
Director, Regulatory Affairs

June 30/2000
Date

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EXCLUSIVITY SUMMARY for NDA # 21-292 SUPPL #

Trade Name Novothyrox **Generic Name** levothyroxine sodium tablets, USP

Applicant Name Genpharm, Inc. **HFD-** 510

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      A Federal Register notice required submission of literature to support NDAs for these uses of levothyroxine sodium tablets. This application contained literature reports to which the firm did not have right of reference. However, on August 21, 2000, FDA approved the first levothyroxine sodium tablets NDA required by the FR. Therefore, the literature were not needed because NDA 21-210 was approved after this NDA was submitted but before this NDA was filed.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe

the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 21-210 Drug Name Unithroid

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement

or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted

or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

{See appended electronic signature}

Preparer: Enid Galliers Date: 26-MAY-2002
Title: Chief, Project Management Staff, DMEDP

{See appended electronic signature}

David G. Orloff, M.D. Date:
Director, DMEDP

cc:
Archival NDA
HFD- 510/RPM
HFD-095/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

David Orloff
5/28/02 07:34:17 PM

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-292 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Complete RsponseStamp Date: 03-DEC-2001 **Action Date:** 03-JUN-2002

HFD 510 **Trade and generic names/dosage form:** NOVOTHYROX (levothyroxine sodium tablets, USP) , 12 strengths

Applicant: GENPHARM, INC. **Therapeutic Class:** thyroid

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: (1) to treat hypothyroidism

Is there a full waiver for this indication (check one)?

XX **Yes:** Please proceed to Section A.

☐ **No: Please check all that apply:** ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ X **Products in this class for this indication have been labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**

- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager
Enid Galliers

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: (2) to suppress thyroid-stimulating hormone

Is there a full waiver for this indication (check one)?

☐ XX **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ X **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager
Enid Galliers

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/s/

Enid Galliers
5/27/02 09:24:34 PM
CSO

This NDA has **not** been approved as of the date of this memo. The goal date is June 3, 2002.

GENPHARM

DEBARMENT CERTIFICATION

I certify that Genpharm Inc. did not and will not use the services of any person debarred under Section 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act, in connection with the development of this drug product and the preparation of this New Drug Application.

I further certify that neither Genpharm Inc. nor any affiliated person responsible in any capacity for providing services or generating information for this New Drug Application for ——— Tablets (Levothyroxine Sodium Tablets, USP) 25, 50, 75, 88,100, 112, 125, 150, 175, 200 and 300 μg, has been convicted of any offense required to be listed under Section 306(k)(2) of the Federal Food, Drug and Cosmetic Act during the past five years.

At this time Genpharm Inc has no person to list who have been convicted during the last five years of any offense required to be listed under Section 306(k)(2) of the Federal Food, Drug and Cosmetic Act.

Tirtho Uppal
Director, Regulatory Affairs

June 30/2000
Date

APPEARS THIS WAY
ON ORIGINAL

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

4 pages

Division of METABOLIC AND ENDOCRINE DRUG PRODUCTS

CONSUMER SAFETY OFFICER LABELING REVIEW

Application Number: NDA 21-292

Name of Drug: Novothyrox (levothyroxine sodium tablets, USP)
25, 50, 75, 88, 100. 112, 125, 137, 150, 175, 200, 300 mcg

Sponsor: Genpharm, Inc.

Material Reviewed:

Submission Date(s): May 27, 2002
Receipt Date(s): May 28, 2002

Background and Summary

This will be the fourth levothyroxine sodium tablets (LT4) NDA to be approved in response to the 1997 Federal Register notice that required approved applications to market LT4 tablets in the U.S. The 1997 FR notice was amended to delay implementation until August 14, 2001. The application covers 12 strengths of LT4.

The indications that will be approved are: treatment of hypothyroidism and suppression of thyroid-stimulating hormone (TSH).

Review

The package insert (PI) was compared to the most recent (04.22.02) template labeling developed by DMEDP. The applicant added required product-specific information.

1. Product-specific CMC information:

DESCRIPTION
Inactive Ingredients
NOVOTHYROX (levothyroxine sodium tablets, USP) contain the following inactive ingredients: corn starch, croscarmellose sodium, gelatin, lactose monohydrate, and magnesium stearate. All strengths of NOVOTHYROX tablets are formulated without color additives for patients who are sensitive to dyes.

HOW SUPPLIED
NOVOTHYROX (levothyroxine sodium tablets, USP) are supplied as off-white, round tablets,

that are flat on both sides with a beveled edge and a cross score on one side. They are available in 12 strengths as follows:

Strength (mcg)	Debossed marking	NDC # for CRC bottles of 5000	NDC # for Unit Dose Cartons of 100
25	"EM" and "25"	NDC 55567-130-37	NDC 55567-130-06
50	"EM" and "50"	NDC 55567-131-37	NDC 55567-131-06
75	"EM" and "75"	NDC 55567-132-37	NDC 55567-132-06
88	"EM" and "88"	NDC 55567-133-37	NDC 55567-133-06
100	"EM" and "100"	NDC 55567-134-37	NDC 55567-134-06
112	"EM" and "112"	NDC 55567-135-37	NDC 55567-135-06
125	"EM" and "125"	NDC 55567-136-37	NDC 55567-136-06
137	"EM" and "137"	NDC 55567-137-37	NDC 55567-137-06
150	"EM" and "150"	NDC 55567-138-37	NDC 55567-138-06
175	"EM" and "175"	NDC 55567-139-37	NDC 55567-139-06
200	"EM" and "200"	NDC 55567-140-37	NDC 55567-140-06
300	"EM" and "300"	NDC 55567-141-37	NDC 55567-141-06

STORAGE CONDITIONS
Store between 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F).

Protect from light and moisture.

MANUFACTURER

Manufactured by:	For:
Merck KGaA	**Genpharm Inc.**
Frankfurter Strasse 250	Toronto, Ontario
64293 Darmstadt	Canada M8Z 2S6
Germany	

This information is acceptable to the review chemist, Dr. David Lewis.

2. The product-specific value for bioavailability is added as listed below:

CLINICAL PHARMACOLOGY, Pharmacokinetics, *Absorption*
. . . The relative bioavailability of NOVOTHYROX tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%.

This value is acceptable to the biopharmaceutics reviewer, Dr. Steve Johnson.

3. Except for product-specific information and several editorial changes made by Genpharm, the submitted labeling is identical to the template labeling. Genpharm's editorial changes included the addition of some implied words that were omitted from the template. The specific differences are noted in color and with underline and strikeout in the attached pdf version of the MS Word electronic comparison. The changes are acceptable. (In Table 2, the firm used ' ——— instead of "thiazolidinedione," which is the term accepted by the Division.) The paper printout of the comparison of the submitted MSWord version to the FDA template omitted the symbols "≥" and "≤." However, the MS Word version and the typeset version submitted to the NDA correctly included them. To have the symbols "≥" and "≤" appear in the attached pdf version of the comparison it was necessary to replace those symbols in the electronic copy submitted by the manufacturer with the symbols available in the CDER standard desktop CPU load, running the MS Word comparison again, and then converting to pdf. (The "α" and "β" were replaced also.) The hard copy Package Insert bears Identifier # 008-465 REV.01; Issued: May 2002).

4. The May 27, 2002, submission also contained modified blister, carton, and bottle labels. Reviews of an earlier version of the labels suggested that the colors used in the pentagonal color blocks located on either side of the tablet strength should not be so similar for adjacent strengths. The firm has modified the colors and they are more easily distinguishable. The May 30, 2002, chemistry review states this is satisfactory.

5. The firm had previously used heavy black lines above and below the trademark on the labels such that the established name was separated from the proprietary name in violation of 21 CFR 201.10(g)(1). The May 27, 2002, labels have corrected this by positioning the lower line below the established name. The May 30, 2002, chemistry review states this is satisfactory.

6. The blister labels, bottle labels, and blister cartons are satisfactory. However, the hard copy labels for the 5000-count bottles of the 25 mcg and 75 mcg strength tablets omit the "degree" (°) symbol between the temperature and F or C. The review chemist does not object to the use of the labels with this omission. The *pdf* versions of the bottle labels submitted by the firm contain the degree symbol on the 5000-ct bottle labels for all strengths. The firm will be notified of this discrepancy by phone.

7. The word "permitted" was added after "excursions" to the STORAGE CONDITIONS statement as requested by the Agency. The May 30, 2002, chemistry review states this is satisfactory.

8. The Identifier # for the different presentations are as follows:

Strength (mcg)	Indentifier # for CRC bottles of 5000	Identifier # for Unit Dose Cartons of 100	Identifier # for Unit Dose Blisters of 10
25			
50			
75			
88			
100			
112			
125			
137			
150			
175			
200			
300			

Conclusions

The package insert and container/carton labels are acceptable.

Reviewer
{See appended electronic signature.}

Enid Galliers
Chief, Project Management Staff, DMEDP

Supervisory Comment/Concurrence:

{See appended electronic signature.}

David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

ATTACHMENT (Comparison of draft Novothyrox labeling with LT4 Ttemplate)

Drafted: EMG/ 05.29,30.2002/
Finalized: E.Galliers/05.31.2002/
Filename: \21292\pmlbg.rev.doc

CSO LABELING REVIEW

Number of Pages Redacted 136

❖❖❖

Draft Labeling
(not releasable

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0250
CONNECTION TEL	914162362940
CONNECTION ID	
ST. TIME	05/31 14:54
USAGE T	07'58
PGS. SENT	24
RESULT	OK

facsimile
TRANSMITTAL

[redacted]

to: Dr. Bonnie Southorn, Director, CTD and Submissions, Genpharm, Inc.
fax #: 416-236-2940
re: NDA 21-292 Novothyrox (levothyroxine sodium tablets, USP)
date: 31 May 2002
pages: 24 (including cover page)

Your Novothyrox application was approved this afternoon. The approval letter is attached.

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 31, 2002

FROM: Eric P. Duffy, Ph.D.
Director, DNDCII, ONDC

SUBJECT: Approval of NDA 21-292
Novothyrox™ (levothyroxine sodium tablets, USP)
Genpharm, Inc.

TO: Docket # 02P-0135/PSA1
NDA 21-292

Jerome Stevens Pharmaceuticals, Inc. (Jerome) submitted a Petition for a Stay of Action, No. 02P-0135/PSA1, dated March 26, 2002, and filed by the Agency on March 28, 2002. The petition requests that FDA immediately and indefinitely stay (1) all grants of drug pre-market authority that were based on New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) that used, relied on, or were based on Jerome's confidential and trade secret manufacturing information for orally-administered levothyroxine sodium (LS) and (2) all pending and prospective NDAs and ANDAs that use, rely on, or are based on Jerome's confidential and trade secret manufacturing information for orally administered LS. Jerome claimed in a Notice of Claims Pursuant to the Federal Tort Claims Act dated March 26, 2002 (Notice) that certain information that had been posted on FDA's Website (http://www.fda.gov/cder/) on August 22, 2000, regarding Jerome's NDA 21-210 for LS was confidential and trade secret information.

The Office of New Drug Chemistry has reviewed Genpharm Inc. (Genpharm's) NDA 21-292, submitted on June 27th, 2000, and has determined that the Genpharm NDA did not use or rely on, and was not based on Jerome's allegedly confidential information. This determination is based on the fact that the batches Genpharm used to support its NDA were manufactured prior to the posting on the agency's website of the approval materials from Jerome's NDA for LS.[1]

[1] The filing of this memorandum solely represents a determination that the Genpharm NDA did not use or rely on, and was not based on Jerome's allegedly confidential information. It does not represent a determination with regard to any other issue, nor does it constitute an admission of any issue raised by Jerome's Petition or Notice.

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/s/

Eric Duffy
5/31/02 04:07:13 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: May 30, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-292
Novothyrox (levothyroxine sodium tablets, USP)
Genpharm

SUBJECT: NDA review issues and action

Background
This application was originally submitted June 27, 2000 and the Division issued an "approvable" letter on May 4, 2001, citing CMC, nomenclature (unacceptable proposed names), and labeling deficiencies and commenting on package labeling and dissolution specifications. The sponsor submitted a complete response on November 29, 2001.

As per the Federal Register of August 14, 1997, with revisions issued in the Federal Register of April 26, 2000, sponsors wishing to continue marketing of levothyroxine sodium containing drug products after August 14, 2001 require approved NDAs for such products. Those sponsors of applications pending before the Agency as of August 14, 2001, have two years to obtain final approval, during which time they must reduce distribution of product according to a prescribed "ramp-down" process such that by August 14, 2003, absent approval, distribution of unapproved LT4 products will cease.

The requirement for NDAs stems from longstanding and repeated instances across numerous manufacturers of LT4 products, of recalls and adverse events related to sub- or super-potent LT4 product. Precision and consistency in dosing are important for the overall safety and efficacy of LT4 products as replacement or suppressive therapy, and the problems of potency and stability have plagued this drug category for years were judged to render the overall class of drugs in need of significant improvements in quality.

Up to August 14, 2001, NDAs for LT4 products could be submitted pursuant to section 505(b)(2) of the FFD&C Act and required no new clinical trial data to establish safety and efficacy, but rather could rely on CMC information addressing drug potency and stability and on bioavailability data.

Genpharm has now submitted full, satisfactory information in support of approval.

Clinical
As above, no new clinical data have been submitted, pursuant to guidance from the Division.

Labeling
The product label proposed conforms to the template label developed by the division for LT4 products. Final labeling has been submitted and is acceptable.

Biopharmaceutics
OCPB finds the bioavailability and "dosage-form equivalence" data acceptable. Dissolution method and tolerance specifications have been established and conveyed in the action letter. Lots used in the biopharmaceutics studies were manufactured prior to August 22, 2000.

Pharmacology/Toxicology
There are no preclinical toxicology issues with this product or with levothyroxine sodium generally.

Chemistry/ Microbiology
The chemistry, manufacturing, and controls are satisfactory and the application may be approved from the standpoint of ONDC. The sponsor has addressed the CMC deficiencies enumerated in the approvable letter. Commercial scale lots of this product are released at 100% of labeled claim. Stability data have been submitted and reviewed and they support a 24-month expiry for all dosage strengths.

Of note, each batch of LT4 tablets used to support the CMC portion of the approval of this NDA was manufactured prior to August 22, 2000.

The establishment inspections were all acceptable.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
The analytical portions of the bioavailability studies were audited by DSI. Minor deficiencies were noted and a Form 483 was issued. DSI concluded that the deficiencies did not affect the validity or acceptability of the data for review.

Financial disclosure
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature
The revised proprietary name, Novothyrox, has been found acceptable by ODS and is likewise acceptable to the Division.

Recommendation
NDA 21-292 may be approved.

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/s/

David Orloff
5/31/02 11:51:11 AM
MEDICAL OFFICER

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MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 29th, 2002

FROM: David B. Lewis, Ph.D.

SUBJECT: **Revised labeling**

TO: NDA 21-292 Division File

Genpharm submitted revised labeling (immediate container label for 5000-count bottles, labeling for unit-dose packaging, including carton, and package insert). The revised labeling was received by CDER (DMEDP, HFD-510) on Tuesday, May 28th, 2002. The revised labeling was done per FDA request, as follows:

- The proprietary name was changed from ——— to Novothyrox.
- The word "permitted" was added to the excursion statement, which now reads "excursions permitted 15° to 30°C". This change was made for the bottle labels, carton labels, and the package insert.
- The color scheme for the immediate container labels (5000-count bottles and blister packs) was changed. The labeling comments, regarding label color schemes identified the following specific problems:
    - The 25, 75, and 88-mcg tablets were highlighted by similar shades of green.
    - The 112 and 150-mcg tablets were highlighted by similar shades of red.
    - The 200 and 137-mcg tablets were highlighted by similar shades of gold/yellow.
- The colors on the labels correspond to the "strength bars", which are arrows highlighting the designation of strength. The color-coding was changed as follows:

Tablet strength	Previous color	Revised color
25-mcg	Slate green	Peach
50-mcg	Light gray	Silver
75-mcg	green	Purple
88-mcg	green	Lime Green
100-mcg	green	Turquoise
112-mcg	Cherry red	Cherry red
125-mcg	Royal blue	French blue
137-mcg	Yellow	Gold
150 mcg	Cherry red	Teal
175 mcg	Burnt orange	Burnt orange
200 mcg	Yellow	Pink
300 mcg	Red	Copper

Comments: The proposed colors for the 300 and 112-mcg tablets (copper and red) are somewhat similar, as are the colors for the 88 and 100-mcg tablets (green and turquoise); however, there is a limit to the number of completely distinguishable colors that could be utilized. The inks for each label are specified. The firm intends to add colorants to their tablets, post-approval via PA supplement.

The package insert was changed as follows:

- DESCRIPTION SECTION: the word "contains" was added to the 1st paragraph, as follows: "NOVOTHYROX (levothyroxine sodium tablets, USP) contains synthetic crystalline ..." This is a grammatical correction, and is acceptable. The proprietary name was changed to NOVOTHYROX (per FDA request), and the Rx only warning was added directly below the established name.

Other comments: The established name is exactly ½ as large as the proprietary name (verified by measuring the capital "T" in NOVOTHYROX and in TABLETS.

Conclusion: The revised labeling for the drug product [Novothyrox (levothyroxine sodium tablets, USP)] is acceptable.

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/s/

David Lewis
5/29/02 03:01:35 PM
CHEMIST
No comment
Here's the memo

Sheldon Markofsky
5/30/02 08:00:49 AM
CHEMIST

GENPHARM

LABELING AMENDMENT

Office of New Drug Chemistry
Division of Metabolic and Endocrine Drug Products, HFD–510
Division Document Control Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Attn: Dr. David Orloff, Division Director

RE: NDA 21-292
Novothyrox (levothyroxine sodium tablets, USP)
25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300 mcg

Genpharm Inc. hereby submits this amendment to our above-referenced NDA in response to labeling comments received from Ms. Enid Galliers, Chief, Project Management Staff on May 9 and 10, 2002 via our U.S. agent.

For the reviewer's convenience, we have presented this amendment in a comment/response format. Ms. Galliers' comments have been presented sequentially in **bold**, followed immediately by the response.

In accordance with 21 CFR § 314.50, we have enclosed one archival copy and one review copy of this submission.

As requested by Ms. Galliers, we are enclosing three sets of labeling in the archival copy and one set of labeling in the review copy. To facilitate review, we are also enclosing two desk copies of the submission, each containing one set of labeling. A diskette containing the package insert in MS Word and bottle container labeling in PDF has been included at the front of the archival copy of this submission. We regret that we are unable to provide electronic copies of the blister and carton labeling at this time. Genpharm Inc. certifies that the electronic version of the package insert contains the same text as the hard copy.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 416-207-1216 or you may contact our U.S. agent, Mr. Eugene Pfeifer or Ms. Christina Markus of King & Spalding, at 202-737-0500

Sincerely,
GENPHARM INC.

Bonnie Southorn, Ph.D.
Director, CTD and Submissions

May 27, 2002
Date

cc. Ms. Christina Markus, King & Spalding
Ms. Friederike von Burkersroda, Merck KGaA

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

FDA COMMUNICATIONS

APPEARS THIS WAY
ON ORIGINAL

KING & SPALDING

1730 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20006-4706
TELEPHONE: 202/737-0500
FACSIMILE: 202/626-3737

DIRECT DIAL:
202/626-2926

EMAIL:
cmarkus@kslaw.com

MEMORANDUM

VIA FACSIMILE

TO: Bonnie Southorn, Ph.D.
Director, CTD and Submissions
Genpharm Inc.

FROM: Christina M. Markus CM

DATE: May 10, 2002

RE: NDA 21-292 -- Levothyroxine Sodium Tablets, USP

I spoke with Enid Galliers of FDA on May 9, 2002 concerning the referenced new drug application (NDA). Ms. Galliers conveyed the following comments and requests:

1. Genpharm should ensure that its package insert is consistent with the most recent FDA template (dated April 22, 2002), a copy of which is attached. Ms. Galliers requested that, if a revised package insert is submitted, it be provided in a labeling amendment including a computer diskette version in MS Word format.

2. Ms. Galliers noted that, due to FDA document room procedures for recording the date of a submission (*i.e.*, if there is a date on the very first page of a submission cover letter, that date is used (the second page of a cover letter is *not* considered); otherwise, the date on the 356h form is used), there are sometimes discrepancies in the dates used to reference individual submissions. To facilitate consistent reference, Ms. Galliers requests that Genpharm present a date on the first page of each submission cover letter.

191 PEACHTREE STREET
ATLANTA, GA 30303-1763
TELEPHONE: 404/572-4600
FACSIMILE: 404/572-5100

1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-4003
TELEPHONE: 212/556-2100
FACSIMILE: 212/556-2222

1100 LOUISIANA STREET, SUITE 4000
HOUSTON, TX 77002-5213
TELEPHONE: 713/751-3200
FACSIMILE: 713/751-3290

3. FDA reviewers have raised two concerns about the color and contrast of Genpharm's proposed product packaging:

   - On bottle labels, there is not enough distinction in shades of color (*e.g.*, yellow/orange, which might be used as a product identifier), particularly for product strengths that are close to one another.

   - On unit dose blister foil backing, there is not enough contrast to easily read some colors (*e.g.*, 112 µg and 150 µg red).

   I expect to receive a facsimile from Ms. Galliers that clarifies one or both of these points, and shall forward it as soon as I receive it.

4. FDA finds the "Novothyrox" name acceptable. This name should be used in your revised package insert.

5. Concerning storage conditions, FDA prefers that the word "permitted" be used to describe excursions (*i.e.*, text would read "excursions permitted 15° to 30° C" (emphasis added)). This pertains to bottle labels, cartons, and the package insert.

Ms. Galliers advised that, if Genpharm revises bottle labels and/or cartons, you should submit five (5) complete sets of color mock-ups and (if available) a computer diskette in PDF format. Both container size presentations should be submitted for all strengths of the product.

As noted above, FDA requests that any revised package insert be submitted on computer diskette in MS Word format.

* * *

Ms. Galliers will be out of the office until Tuesday, May 14. Her telephone number is 301-827-6429 should you wish to speak with her directly. In the meantime, please contact me if you should have questions.

Attachment

APPEARS THIS WAY
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Galliers, Enid M

rom: Galliers, Enid M
Sent: Thursday, May 09, 2002 5:36 PM
To: 'cmarkus@kslaw.com'
Subject: Revised labeling information

Ms. Markus:

The attached MS Word document contains the recently edited and corrected version of the labeling template for the package insert (PI) for levothyroxine sodium tablets products. The applicant needs to be sure that the NDA has been amended using this version of the PI and the Novothyrox name. We will need to have a submission of the labeling (PI) in hard copy (duplicate) to the NDA accompanied by one diskette containing the PI in MS Word.

Levotemp.late-new.doc

Information regarding requests for changes to the bottle labels and cartons will be sent by fax. Those changes need to be documented by hard copy submission of all presentations for all strengths in color (three sets in the original amendment and one set in the duplicate copy). If it is possible to submit the revised labels in pdf, please submit that with the paper original.

We need to take an action on the application by the end of May.

Sincerely yours,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone: 301-827-6429
Fax: 301-443-9282
email: galliers@cder.fda.gov

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/s/

Enid Galliers
5/9/02 06:39:14 PM
CSO

The MS Word attachment in the email contains the 4.22.2002 version of the levothyroxine sodium tablets PI template.

Number of Pages Redacted 14

❖❖❖

Draft Labeling
(not releasable

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 9, 2002

To: Ms. Christina Markus.	**From:** Enid Galliers
Company: . King & Spalding, US Agent for Genpharm Inc	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 202-626-3737	**Fax number:** 301-443-9282
Phone number: 202-737-0500	**Phone number:** (301) 827-6429

Subject: Discipline Review (CMC) Completed for NDA 21-292 Novothyrox
Revisions to bottle labels and cartons

Total no. of pages including cover: 3

Comments:

See page 2.

Document to be mailed: ☐ YES ☑ NO

Attachment

Comments:

Regarding your pending NDA 21-292 for levothyroxine sodium tablets, we accept your proposed name of NOVOTHYROX.

However, some of the container labels and carton labels use very similar colors for different strengths. That is, the 25 mcg, 75 mcg, and 88 mcg are highlighted by similar shades of green; the 112 mcg and 150 mcg are highlighted by similar shades of red; the 200 mcg and 137 mcg are highlighted by similar shades of gold/yellow. The similarities in color between the strengths greatly increase the potential risk of a medication error occurring between the different strengths. We request that you change the colors so that the label for each strength has a distinctly different color from all the other strengths.

This change to the labels should be done as an amendment to the NDA with four complete color sets of mocked-up labels and cartons for all presentations (100 count unit dose and bottles of 5000.)

Contact Enid Galliers at 301-827-6429 if you have any questions.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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/s/

Enid Galliers
5/9/02 06:23:14 PM
CSO

David Orloff
5/9/02 06:28:08 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Galliers, Enid M

rom: Beam, Sammie
Sent: Thursday, May 09, 2002 8:47 AM
To: Galliers, Enid M
Subject: RE: 90-day Name Consult for NDA 21-292 NOVOTHYROX (levothyroxine sodium tablets); Sponsor = GENPHARM INC.

Hi,

No, we do not need to see this name again unless the approval is delayed (for some reason) until after 7/1/02.

Thanks,
Sammie

-----Original Message-----
From: Galliers, Enid M
Sent: Wednesday, May 08, 2002 8:47 PM
To: Beam, Sammie
Cc: McCort, Stephen M
Subject: 90-day Name Consult for NDA 21-292 NOVOTHYROX (levothyroxine sodium tablets); Sponsor = GENPHARM INC.

Sammie:

Please confirm, if possible, that another (i.e., 90-day) consult request is not needed for this drug name.

This division received a completed DMETS consult that was signed by Jennifer Fan on 3/29/02 and by Carol Holquist on 4/1/02. It stated that the consult was not final and that a 90-day pre-approval consult should be sent. However, the goal date for the NDA was less than 90 days in the future at the time the consult was signed by DMETS. We do intend to approve this NDA, and we would like to act on May 17 because several other NDAs are due on the PDFUA date for this one (and this one is almost ready except for the resubmission of the package insert.

PDUFA date= 06.03.2002
ACTION GOAL DATE = **05.17.2002**

Thank you,

Enid
x76429

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/s/

Enid Galliers
5/27/02 05:57:13 PM

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05.08.02

Note to the file for **NDA 21-292**

Drug: Novothyrox (levothyroxine sodium tablets)

Applicant: Genpharm Inc.

Several submission dates have been changed in COMIS so that our references will be to the dates used by the sponsor. This may affect the dates of submissions referenced by reviewers in their reviews of this NDA.

The following is the instruction to revise the "Letter dates" for three amendments.

Please change the letter dates for the following submissions:

N21-292, N-000-AZ, letter date 03-Dec-2001, change letter date to 29-Nov-2001.
N21-292, N-000-BC, letter date 15-March-2002, change letter date to 13-March-2002
N21-292, N-000-BC, letter date 26-Feb-2002, change letter date to 25-Feb-2002.

Enid Galliers
CPMS. DMEDP

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/s/

Enid Galliers
5/8/02 06:46:44 PM
CSO

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04.25.02

NDA: 21,292
Drug: Levothyrox/Novothyrox
Sponsor: Genpharm, Inc.
Date: April 25, 2002

MEMO TO FILE

Dr. S. Markofsky discussed with Dr. Parks and myself the March 12, 2002 consult received from the Office of Drug Safety pertaining to Levothyrox. In this consult, Dr. Fan expressed concern regarding the color similarities among various dosage strengths. It was agreed that the different dosage strengths should be readily distinguishable, one from the other to avoid potential dosing errors. For example, overdosing errors could pose potential safety concerns for an elderly cardiovascular patient with thyroid disease who is taking levothyroxine sodium tablets.

Jean Temeck. M.D.

cc. HFD-510: Dr. Parks, Dr. Markofsky, Dr. Lewis and Mr. McCort

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/s/

Jean Temeck
4/25/02 04:36:53 PM
MEDICAL OFFICER

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ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 12/20/00	**DUE DATE:** 04/21/01	**OPDRA CONSULT #:** 01-0057

TO:
David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:
Steve McCort
Project Manager
HFD-510

PRODUCT NAME: ——— (levothyroxine sodium tablets, USP) 25 mcg, 50 mcg, 75 mcg, 88 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg **NDA:** 21-292	**MANUFACTURER BY:** Merck KGaA, Darmstadt, Germany **SPONSOR**: Genpharm Inc. Toronto, Canada

SAFETY EVALUATOR: David Diwa Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic & Endocrine Drug Products (HFD-510), OPDRA has performed a review of the proposed proprietary name ——— to determine the potential for confusion with marketed drug products and pending drug names.

OPDRA RECOMMENDATION:
OPDRA does not recommend the use of the proprietary name ———

APPEARS THIS WAY
ON ORIGINAL

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 03/22/01

NDA: 21-292

NAME OF DRUG: ——— (levothyroxine sodium tablets, USP)

NDA HOLDER: Genpharm Inc,

MANUFACTURER: Merck KGaA

I. INTRODUCTION

This consult is written in response to a February 21, 2001 request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proposed proprietary name, ——— Although oral levothyroxine drug products have been on the market since the 1950's, the FDA announced in the Federal Register Notice of August 14, 1997 that orally administered products containing levothyroxine sodium are new drugs. The agency has established a cutoff date of August 14, 2001, after which all oral levothyroxine drug products must be the subject of an approved New Drug Application. The first NDA (21-210) was approved for Unithroid (levothyroxine sodium tablets, USP) on August 21, 2000.

During the review of the proprietary name Unithroid, OPDRA observed that ——— had the most potential for name confusion with proposed name.[1] ——— was also the proprietary name that was utilized for tablets containing liothyronine (T_4) and thyroxine (T_3). However, at that time it was felt that the risk of product name confusion was minimal since ——— products were withdrawn from the U.S. market in 1993. ——— not only contained different active ingredients but was also formulated in different dosage strengths (60 mcg T_4/15 mcg T_3, 120 mcg T_4/30 mcg T_3, 180 mcg T_4/45 mcg T_3). Additionally, prescriptions for Unithroid would require a dose specification that was different from the ——— dosage strengths.

PRODUCT INFORMATION

——— (levothyroxine sodium tablets, USP) is a synthetic tablet formulation of tetraiodothyronine sodium (T_4). It is indicated for use as replacement or supplemental therapy in patients with hypothyroidism, except in cases of transient hypothyroid states during the recovery phase of subacute thyroiditis. The drug is also indicated for use as a pituitary TSH suppressant in the treatment or prevention of various euthyroid goiters including thyroid nodules, subacute and chronic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter. Additional indications include use in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

[1] OPDRA Consult 00-0046, Unithroid NDA 21-210 Proprietary Name Review

[redacted] is contraindicated in patients with untreated thyrotoxicosis and uncorrected adrenal insufficiency. The sponsor recommends a once daily dose of approximately 1.6 mcg/kg for replacement therapy in younger, healthy adults. Elderly patients should be given 1 mcg/kg once a day. The dose of [redacted] in pediatric hypothyroidism will vary with age and body weight. The sponsor proposes supplying [redacted] in blisters of 10 in cartons of 100 and child resistant closure bottles of 5000 tablets. [redacted] will be formulated without color additives and marketed in strengths of 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[2,3,4] as well as several FDA databases[5] for existing drug names which sound alike or look alike to [redacted] to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[6]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies and one verbal prescription study, involving health care practitioners within the FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed name [redacted].

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The panel identified Unithroid as the most problematic in terms of the potential for look-alike/sound name confusion. A summary of the identified product is provided in the table below.

DDMAC expressed no objection to the proposed name [redacted]

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
[redacted]	Levothyroxine sodium tablets, USP	12.5 to 300 mcg/day per pt response	
Unithroid	Levothyroxine sodium tablets, USP	12.5 to 300 mcg/day per pt response	*LA/SA

*SA = Sound-alike
*LA = Look-alike

[2] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[3] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[4] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[5] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[6] WWW location http://www.uspto.gov/tmdb/index.html. The US Patent & Trademark Office Trade Mark Electronic Search System (TESS)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

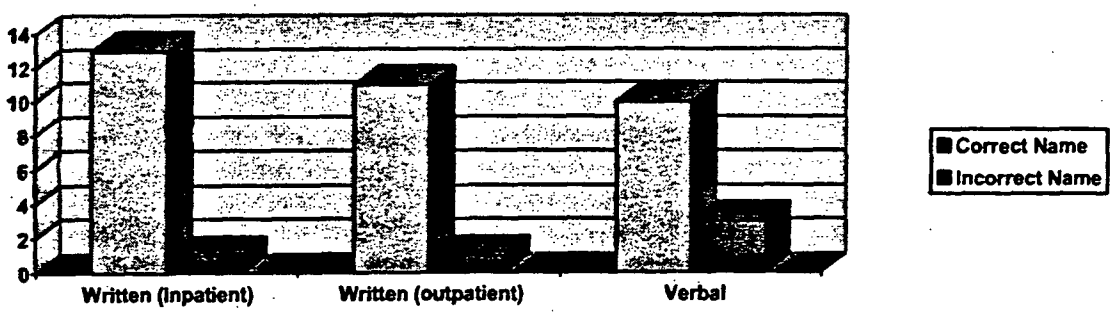
Three studies were conducted by OPDRA involving 86 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between —— and other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for —— (see below). These prescriptions were scanned into a computer and subsequently delivered to a random sample of the participating health professionals via e-mail. In addition, a verbal order was recorded on voice mail. The voice mail message was then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX: —— 100 mcg q AM	Verbal RX: ——. 100 mcg QAM
Outpatient RX: —— 100 mcg i po QAM #30 Refill(s): 2	

2. The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	28	14 (50%)	13 (93%)	1 (7%)
Written Outpatient	28	12 (43%)	11 (92%)	1 (8%)
Verbal	30	13 (43%)	10 (77%)	3 (23%)
Total	86	39 (45%)	34 (87%)	5 (13%)



Thirteen percent of all study participants interpreted the name —— incorrectly. Written and verbal scores of the incorrect responses are summarized in Table II (see page 5).

Table II

Incorrectly Interpreted	
Written Inpatient	[redacted]
Written Out patient	[redacted]
Verbal	Uthroid (3)

All incorrect responses were misspelled or phonetic variations of the proposed drug name. In the verbal study, the first letter [redacted] was omitted from the name [redacted] in all three incorrect responses. Additionally, there were fewer incorrect responses in the two written studies as compared to the verbal study. The inaccurate interpretations of the proposed drug name did not overlap with any existing drug product. Although we did not detect confusion between Unithroid and [redacted] in these studies, we did detect confusion in the Unithroid prescription studies conducted in July 2000, as 2 out 14 respondents misinterpreted the proposed name as [redacted]

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name, the expert panel was most concerned with the close sound-alike/look-alike qualities between [redacted] and Unithroid. We are also concerned that our verbal studies revealed strong sound-alike qualities between [redacted] and Unithroid as 3 respondents interpreted [redacted] as "Uthroid"

Unithroid is an oral tablet formulation containing levothyroxine sodium in strengths of 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 150 mcg, 175 mcg and 300 mcg. [redacted] contains the same active ingredients, will be available in the same dosage strengths, and have the same indications for use as Unithroid. In the proposed formulation, [redacted] and Unithroid would pose a high risk for name confusion.

In addition [redacted] is still listed in reference databases such as Micromedex and the Orange Book. The listings specify that [redacted] is not currently marketed however, it would be confusing if a new product with similar pharmacologic activity is marketed under the same proprietary name. Practitioners unfamiliar with the drug product post launch might utilize a reference text that contains the old formulation of [redacted] and dispense a generic substitute in its place. Furthermore, the US Patent and Trademark Office currently lists [redacted] as a live thyroid preparation patent [redacted]

We acknowledge the sponsor's decision to formulate all strengths of [redacted] tablets without color additives for patients who are sensitive to dyes. However, we believe the lack of tablet color may contribute to medication error. It is a common clinical pharmacy/nursing practice to utilize the tablet color as a quality assurance check prior to dispensing levothyroxine sodium products due to the various dosage strengths. In addition, this serves as a quality assurance check for the patient as well. Unithroid utilizes the same tablet color coding, container labels and carton labeling as Synthroid. Moreover, the 50 mcg tablet for each product is white in color. To minimize the risk of product confusion, we recommend that the sponsor reformulate the tablets to provide a similar color scheme.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of [redacted], OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels, carton and insert labeling and identified several areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENT

   a. Revise the expression of strength to read as "mcg" rather than "µg" or provide both mg and mcg conversion such as "100 mcg (0.1 mg)".

   b. We believe the levothyroxine sodium tablets colors provide a safety link to the proper identification of product strength. Other products, which utilize color to identify product strengths, are Lanoxin, Coumadin, and Premarin. We request the tablets be reformulated to include colors that correspond to the tablet strengths of Unithroid. In addition, the container labels and carton labeling should be revised to match each strength color as well.

2. BLISTER LABELS (10s) and CONTAINER LABELS (5000)

   a. See general comments above.

   b. Placement of the lot number and expiration date directly below the dosage strength on the blister pack foil backing visually crowds the appearance of the dosage strength. Relocate lot number and expiration date or insert a space between the strength and lot number.

3. CARTON LABELING (100 tablets unit dose, Blisters of 10 in cartons of 100)

   See general comments.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name ——. In addition, OPDRA recommends implementation of the above labeling revisions to minimize potential user error.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have any questions or need clarifications, please contact David Diwa at 301-827-0892.

/S/

David Diwa, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur: /S/

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

/s/

David Diwa
4/6/01 02:47:28 PM
PHARMACIST

Jerry Phillips
4/6/01 03:03:06 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 1/7/02	DUE DATE: 3/29/02	ODS CONSULT #: 01-0057-1

TO:

David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

Steve McCort
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:	**NDA SPONSOR:** Genpharm Inc.
——— Novothyrox (Levothyroxine Sodium Tablets) 25 mcg, 50 mcg, 75 mcg, 88 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg **NDA #:** 21-292	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name ——— and "Novothyrox" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS does not recommend the use of the proprietary name ——— ; however, DMETS has no objection to the use of the proprietary name, "Novothyrox". In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

/S/

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 12, 2002

NDA NUMBER: 21-292

NAME OF DRUG: ——— . or Novothyrox (Levothyroxine Sodium Tablets)
25 mcg, 50 mcg, 75 mcg, 88 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg

NDA HOLDER: Genpharm Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradenames ' ——— and "Novothyrox", regarding potential name confusion with other proprietary/established drug names. Prior to this submission, the sponsor had submitted the proprietary name ' ——— ' (OPDRA Consult 01-0057), which was found unacceptable by DMETS.

Levothyroxine drug products were introduced to the U.S. market before 1962 without an approved New Drug Application (NDA). On August 14, 1997, the FDA announced through the Federal Register Notice (Volume 62, No. 157) that all orally administered levothyroxine sodium drug products are new drugs and, therefore, are subject to an approved NDA after August 14, 2000. Currently, *Unithroid* (approved August 21, 2000), *Levoxyl* (approved May 25, 2001), and *Levo-T* (approved March 1, 2002) are approved for the U.S. market.

PRODUCT INFORMATION

——— /"Novothyrox" is the proposed proprietary name for levothyroxine sodium tablets. It is a synthetic formulation of tetraiodothyronine sodium (T_4) and is considred a narrow therapeutic index drug ——— "Novothyrox" is indicated for use as replacement or supplemental therapy in patients with hypothyroidism, except in cases of transient hypothyroid states during the recovery phase of subacute thyroiditis. The drug is also indicated for use as a pituitary TSH suppressant in the treatment or prevention of various euthyroid goiters including thyroid nodules, subacute and chronic lymphocytic thyroiditis (Hashimoto's) and multinodular goiter. Additional indications include use in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid. This drug product is contraindicated in patients with untreated thyrotoxicosis and uncorrected adrenal insufficiency. The recommended dose for adults and children whose growth and puberty are complete is approximately 1.7 mcg/kg/day (100-125 mcg/day for a 70 kg adult). The dose should be taken in the morning on an empty stomach. Elderly patients may require less than 1 mcg/kg/day. The recommended dose for pediatric hypothyroidism will vary with age and weight. ——— /"Novothyrox" will be available as a 25 mcg, 50 mcg, 75 mcg,

88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg tablet. It will be supplied in blisters of 10 tablets in cartons of 100 as well as bottles of 5000 tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to [redacted] and "Novothyrox" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the data provided by [redacted] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies of each proposed proprietary name consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names [redacted] and "Novothyrox". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Regarding [redacted], the panel had concerns with the use of most of the established name as the proprietary name. Also, [redacted] was considered to be a sound-alike and look-alike to [redacted] Regarding "Novothyrox", the panel had concerns with the use of the prefix "novo", which is usually associated with insulin products. These products of concern are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

2. DDMAC had no concerns with [redacted] and "Novothyrox".

[1] MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2001).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov.

[5] WWW location http://www.thomson-thomson.com.

Table 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Novothyro	Levothyroxine Sodium (Rx) Tablet: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	
Levothroid	Levothyroxine Sodium (Rx) Tablet: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	*SA/LA
Novolin R	Regular, Human Insulin Injection (recombinant DNA origin) (OTC) Injection 10 mL vial: 100 units/mL PenFill 1.5 mL and 3mL Cartridges: 100 units/mL Prefilled 1.5 mL Disposable Insulin Delivery System: 100 units/mL	0.5 to 1 unit/kg/day in divided doses	*SA
Novolin 70/30	70% NPH, Human Insulin Isophane Suspension/30% Regular, Human Insulin Injection (recombinant DNA origin) (OTC) Injection 10 mL vial: 100 units/mL PenFill 1.5 mL and 3mL Cartridges: 100 units/mL Prefilled 1.5 mL Disposable Insulin Delivery System: 100 units/mL	0.5 to 1 unit/kg/day in divided doses	*SA
Novolin N	NPH, Human Insulin Isophane Suspension (recombinant DNA origin) (OTC) Injection 10 mL vial: 100 units/mL PenFill 1.5 mL and 3 mL Cartridges: 100 units/mL Prefilled 1.5 mL Disposable Insulin Delivery System: 100 units/mL	0.5 to 1 unit/kg/day in divided doses	*SA
Novolin L	Lente, Human Insulin Zinc Suspension (recombinant DNA origin) (OTC) Injection 10 mL vial: 100 units/mL	0.5 to 1 unit/kg/day in divided doses	*SA
NovoLog	Insulin Aspart (rDNA origin) Injection (Rx) Injection 10 mL vial: 100 units/mL PenFill 3 mL Cartridges: 100 units/mL	0.5 to 1 unit/kg/day in divided doses	*SA

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Novothyro	Levothyroxine Sodium (Rx) Tablet: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	
NovoLog Mix 70/30	70% Insulin Aspart/30% Insulin Aspart Protamine (Rx) Injection 10 mL vial: 100 unites/mL PenFill 3 mL Cartridges: 100 units/mL Prefilled 3 mL Syringe: 100 units/mL	0.5 to 1 unit/kg/day in divided doses	*SA

*Frequently used, not all-inclusive.
**SA (sound-alike), LA (look-alike)

3. Further research revealed other proprietary names that were of concern. Those name are listed in Table 2.

Table 2

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Novothyro	Levothyroxine Sodium (Rx) Tablet: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	
Levoxyl	Levothyroxine Sodium (Rx) Tablet: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	*SA/LA
Levo-T	Levothyroxine Sodium (Rx) Tablet: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	*SA/LA
Ciclopirox	Loprox (brand name) (Rx) Cream: 0.77% Lotion: 0.77%	Apply to affected area twice daily.	*SA

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
—— /Novothyro	Levothyroxine Sodium (Rx) Tablet: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	100 mcg - 125 mcg/day (range: 12.5 mcg - 300 mcg/day per patient response)	
Lovenox	Enoxaparin Sodium (Rx) Injection: 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL, 90 mg/0.6 mL, 120 mg/0.8 mL, 150 mg/1 mL	DVT Prohylaxis *Hip/Knee Replacement:* 30 mg SQ every 12 hours. *Abdominal Surgery:* 40 mg SQ once daily. DVT Treatment & Unstable Angina/Non-Q-wave MI: 1 mg/kg SQ every 12 hours	*SA

*Frequently used, not all-inclusive.
**SA (sound-alike), LA (look-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six studies were conducted by DMETS and involved a total of 115 health care professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of '——' and "Novothyrox" with other drug names due to the similarity in visual appearance with handwritten prescriptions and verbal pronunciation of the name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for '——' and "Novothyrox" (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

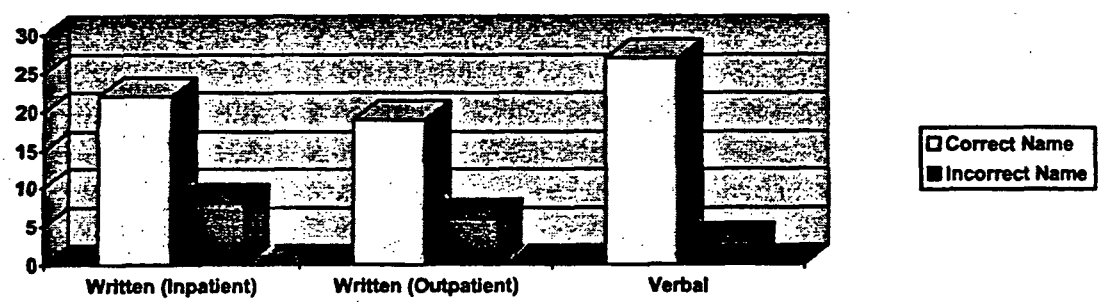
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx: [illegible] 88 mcg qd	*Outpatient Rx:* —— 88 mcg po qd, #30.
Outpatient Rx: —— 88 mcg po qd #30	

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
"Novothyrox"	
Inpatient Rx: Start Novothyrox 25mcg QAM	*Outpatient Rx:* Novothyrox 25 mcg. Take 1 by mouth every morning. #30
Outpatient Rx: Novothyrox 25mcg Sig: 1 PO qam #30	

2. Results:

a) *Results of the " " exercises are summarized below:*

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	40	30 (75%)	22 (73%)	8 (27%)
Written Outpatient	35	25 (71%)	19 (76%)	6 (24%)
Verbal: Outpatient	40	30 (75%)	27 (90%)	3 (10%)
Total	115	85 (74%)	68 (80%)	17 (20%)



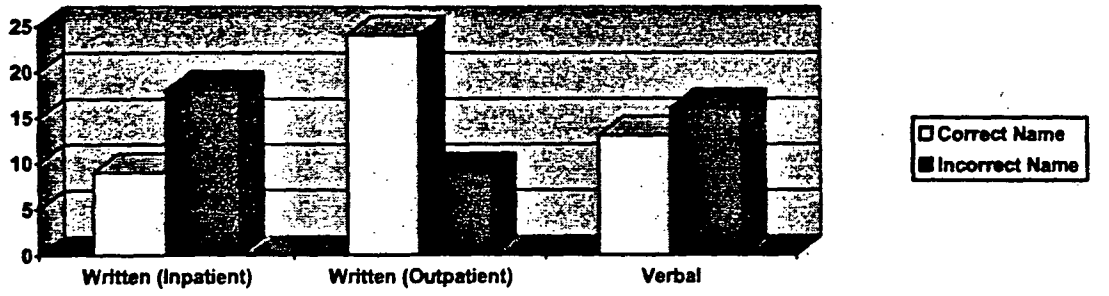
Among the written inpatient prescriptions, 8 (27%) out of 30 respondents interpreted " " incorrectly. Two (7%) respondents interpreted " ".

Among the written outpatient prescriptions, 6 (24%) out of 25 respondents interpreted " " incorrectly. Two (8%) respondents interpreted " ".

Among the verbal outpatient prescriptions, 3 (10%) out of 30 respondents interpreted [redacted]" incorrectly. Interpretations included [redacted]

b) *Results of the "Novothyrox" exercises are summarized below:*

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Novothyrox"	Incorrectly Interpreted
Written Inpatient	35	27 (77%)	9 (33%)	18 (67%)
Written Outpatient	40	33 (83%)	24 (73%)	9 (27%)
Verbal: Outpatient	40	29 (73%)	13 (45%)	16 (55%)
Total	115	89 (77%)	46 (52%)	43 (48%)



Among the written inpatient prescriptions, 18 (67%) out of 27 respondents interpreted "Novothyrox" incorrectly. Interpretations included [redacted]

Among the written outpatient prescriptions, 9 (27%) out of 33 respondents interpreted "Novothyrox" incorrectly. Interpretations included [redacted]

Among the verbal outpatient prescriptions, 16 (55%) out of 29 respondents interpreted "Novothyrox" incorrectly. Interpretations included [redacted]

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary names [redacted] and "Novothyrox", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names include *Ciclopirox, Lovenox, Levothroid, Levoxyl, Levo-T, Novolin (R, 70/30, N, and L), NovoLog, and NovoLog Mix 70/30.*

Ciclopirox is the established name for *Loprox* and is indicated for tinea pedis, tinea cruris, and tinea corporis due to *T. rubrum, T. mentagrophytes, E. floccosum, and M. canis.* It is also indicated for cutaneous candidiasis due to *C. albicans* and tinea versicolor due to *M. furfur. Loprox* is available as a 0.77% topical cream and lotion. *Ciclopirox* sounds similar to both [redacted] and "Novothyrox" due to the similarity in the pronunciation of the last two syllables ("pirox" and "thyrox") and contains the same number of syllables in the proprietary

names (4 syllables). However, they differ in route of administration (topical vs. oral), dosage form (cream and lotion vs. tablet), directions of use (apply twice daily vs. take by mouth once daily in the morning), expression in strength (% vs. mcg), and strength (0.77% vs. 25 mcg, 50 mcg, 75 mcg, 88 mcg, etc.). These differences will decrease the potential risk of confusion between *Ciclopirox* and [illegible] /"Novothyrox".

Lovenox is the proprietary name for enoxaparin sodium and is indicated for the prophylaxis and treatment of deep vein thrombosis (DVT) as well as for the prevention of ischemic complications of unstable angina and non-Q-wave MI. It is available as 30 mg/0.3 mL, 40 mg/0.4 mL, 80 mg/0.8 mL, 100 mg/mL, 90 mg/0.6 mL, 120 mg/0.8 mL, and 150 mg/mL injection. *Lovenox* sounds similar to [illegible] since both proprietary names begin with the "l" sound, have the "v" sound in the middle of the proprietary name, and end in "ox". However, both proprietary names contain different number of syllables (3 vs. 4). There are overlapping strength numbers (100 and 150). Even though the strength expressions are different (mg/mL vs. mcg) especially when pronounced verbally, "mcg" may sometimes be misinterpreted as "mg". A prescriber may also sometime express "mg/mL" as just "mg". *Lovenox* and [illegible] have different dosage forms (injection vs. tablet) as well as different route of administration (subcutaneous vs. oral). However, there have been cases where injections have been confused with oral drug products such as *Celebrex* (capsule) and *Cerebyx* (injection). If a patient mistakenly receives *Lovenox* instead of " [illegible] ", then the patient's hypothyroid condition would not be treated. Also, the patient would be exposed to unnecessary side effects such as bleeding events and thrombocytopenia. If the patient mistakenly receives " [illegible] " instead of *Lovenox*, then prophylaxis or treatment of the patient's DVT or of ischemic complications of unstable angina and non-Q-wave MI would not occur. The patient would be exposed to unnecessary side effects of " [illegible] " such as angina, tachycardia, and arrhythmias.

Levothroid is the proprietary name for levothyroxine sodium and was available in the U.S. market before August 14, 2000. [illegible] may not presently be confused with *Levothroid* due to the availability of *Levothroid*, but if *Levothroid* is brought back into the U.S. market, confusion between *Levothroid* and [illegible] may occur. *Levothroid* sounds similar to [illegible] ." since both proprietary names begin with "levoth". Both drug products have the same strengths, the same dosage form (tablet), the same route of administration (oral), and the same direction of use (take in the morning). Even though it has the same active ingredient as [illegible] , it may not be bioequivalent to [illegible] ." and, therefore, not interchangeable with one another. Since levothyroxine sodium is a narrow therapeutic index (NTI) drug, a slight increase or decrease of the drug strength would result in adverse reactions. If *Levothroid* had a lower potency than [illegible] of the same strength and the patient mistakenly receives *Levothroid* instead of [illegible] , then the patient's disease would not be adequately treated (ie. hypothyroid sequelae). If the patient mistakenly receives [illegible] instead of *Levothroid*, thereby receiving a superpotent dose, the patient may experience angina, tachycardia, and/or arrhythmias.

Levoxyl and *Levo-T* are the proprietary names for levothyroxine sodium and are currently available in the U.S. market. *Levoxyl* sounds and looks similar to " [illegible] ." since both proprietary names begin with "Levo" and contain "ox". *Levo-T* may be mistaken for an abbreviation of " [illegible] ." and/or "levothyroxine". The issues of confusion are the same as the above-mentioned *Levothroid*. *Levoxyl, Levo-T,* and [illegible] may not be bioequivalent to each other. Same strengths of *Levoxyl, Levo-T,* [illegible] ." may show different levels of potency, and since levothyroxine sodium is a NTI, the different levels of potency would affect the safety and effectiveness of the drug product.

The proprietary name ' ——— is contained in the established name ' ———
In the three studies conducted by DMETS, 4 (5%) out of a total of 85 respondents interpreted ——— ' as *Levothyroxine*. Two respondents interpreted ' ——— ' as *Levothryoxine* and *Levothyroxin*, which are similar in spelling of *Levothyroxine*. A prescription for ——— ' may be interpreted for a prescription of any brand name of levothyroxine sodium (currently, *Levoxyl, Unithroid,* and *Levo-T)*. If a pharmacist does not have access to a patient's drug history, such as in a polypharmacy situation, then the patient may receive a different brand name of levothyroxine sodium that is not bioequivalent to the patient's current drug. Since levothyroxine sodium is a NTI drug, a slight increase or decrease of the drug strength would result in adverse reactions. If the wrong levothyroxine sodium had a lower potency than the patient's current medication of the same strength and the patient mistakenly receives the wrong medication, then the patient's disease would not be adequately treated (ie. hypothyroid sequelae). If the patient receives a higher potency, the patient may experience angina, tachycardia, and/or arrhythmias.

Additionally, one respondent in the written outpatient portion of the ——— ' DMETS study interpreted ' ——— as *Levoquin*, which is similar in spelling to *Levaquin*. *Levaquin* is the proprietary name for levofloxacin and is indicated for the treatment of susceptible microorganisms causing acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections, complicated and uncomplicated urinary tract infections, and acute pyelonephritis. *Levaquin* is available as a 250 mg, 500 mg, and 750 mg tablet as well as a 500 mg and 750 mg injection concentrate and 250 mg, 500 mg, and 750 mg premix injection. The recommended doses range from 250 mg - 750 mg every 24 hours. The "levo" and "leva" may look similar; however, the "th" in '. ——— ' may distinguish it from *Levaquin*. Both are available in an oral dosage form (tablet) and have the same directions of use (once a day). Even though there are no overlapping strengths, they do overlap in strength numbers. For example, "250 mg", "500 mg", and "750 mg" (*Levaquin*) can be mistaken for "25.0 mcg", "50.0 mcg", and "75.0 mcg" ———). Also, when scripted, "mcg" can be mistaken for "mg" and vice versa. If a patient mistakenly receives *Levaquin* instead of ' ——— .", then the patient's hypothyroid condition would not be treated. The patient would be exposed to unnecessary side effects of "Levaquin" such as dizziness, headache, insomnia, nausea and vomiting, thrombocytopenia, and tremmors. If the patient mistakenly receives ——— ' instead of *Levaquin*, then the patient's infection would not be treated. Also, the patient would be exposed to unnecessary side effects of ' ——— such as angina, tachycardia, and arrhythmias.

Novolin and *NovoLog* are proprietary names for insulin products. Depending on which *Novolin* the patient uses, the patient may inject the drug product once a day to three times a day while *NovoLog* is injected three times a day before meals. *Novolin, NovoLog*, and "Novothyrox" sound similar due to the prefix "Novo-". However, the "thyrox" in "Novothyrox" may differentiate it enough from *Novolin* and *NovoLog* so that the potential risk of confusion would be decreased. Even though *Novolin* and "Novothyrox" may overlap in dosing regimen (once a day), there is no overlap in dosing regimen between *NovoLog* and "Novothyrox". Also, the difference in dosage forms (injection vs. tablet) and the route of administrations (subcutaneous vs. oral) may decrease the potential risk of confusion between these drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. GENERAL COMMENT

1. In regards to the color consistency of the tablets, container labels, and carton labeling to other levothyroxine sodium drug products, refer to Labeling, Packaging and Safety Related Issues, General Comment (b) in OPDRA Consult 01-0057 dated 4/6/01.

2. Some of the colors on the container labels and carton labeling that indicate the different strengths are very similar. The 25 mcg, 75 mcg, and 88 mcg are highlighted by similar shades of green. The 112 mcg and 150 mcg are highlighted by similar shades of red. The 200 mcg and 137 mcg are highlighted by similar shades of gold/yellow. These similarities in color between the strengths highly increases the potential risk of a medication error occurring between the different strengths. We recommend highlighting the strength with the same color utilized for each tablet strength.

B. BLISTER PACKAGE (25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg)

1. See GENERAL COMMENTS.

2. Refer to OPDRA Consult 01-0057, Blister Labels and Container Labels, comment (b).

3. The black lettering on a green background (25 mcg, 75 mcg, and 88 mcg) may make it difficult to read the drug name and strength. The lettering should either be lighter than the background or the background should be lighter in color than the print.

C. CONTAINER LABEL (5000 tablets: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg)

See GENERAL COMMENTS.

D. CARTON LABELING

1. See GENERAL COMMENTS.

2. The size and placement of the "Rx only" statement appears with the same prominence as the product strength. The statement should be in a smaller font size, and a space should be inserted between the strength and the "Rx only" statement.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name ——— ; however, DMETS has no objections to the use of the proprietary name "Novothyrox".

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's/ANDA's from this date forward.

B. DMETS recommends implementation of the labeling revisions outlined in section III that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Jennifer Fan
3/29/02 04:15:35 PM
PHARMACIST

Carol Holquist
4/1/02 07:47:48 AM
PHARMACIST

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

3 pages

Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: 3-05-02

To: Bonnie Southern	**From:** Steve McCourt
Company: Gen Pharm	Division of Metabolic and Endocrine Drug Products
Fax number: 416-236-4365	**Fax number:** (301) 443-9282
Phone number: 416-207-1216	**Phone number:** 301-827-6615

Subject: L-Thyroxine Sodium Tablets

Total no. of pages including cover:

Comments: If you have any questions, feel free to call Steve McCourt, Project Manager.

Document to be mailed: ☐ YES ☑ NO

REVISIONS TO FDA's LEVOTHYROXINE SODIUM LABELING TEMPLATE:

1. PRECAUTIONS section: Effects on bone mineral density:
   Replace the first sentence with the following:
   In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels.

2. Pregnancy section:
   Revise the beginning of the first sentence in the third paragraph to read: "Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood…

3. ADVERSE REACTIONS section:
   Add: (see PRECAUTIONS and OVERDOSAGE) at the end of the first sentence.
   Replace "Cardiac" with "Cardiovascular";
   Replace "Pulmonary" with "Respiratory";
   Replace "GI" with "Gastrointestinal" and add: "elevation in liver function tests".
   After Dermatologic, add "Endocrine: decreased bone mineral density".

4. OVERDOSAGE section:
   Replace "approximately 20 mg" with "18 mg" in the fourth sentence of the first paragraph.
   Acute Massive Overdosage- Revise the fourth sentence to read: "Central and peripheral increased sympathetic activity may be treated by administering β-receptor antagonists, e.g. propranolol, provided there are no medical contraindications to their use". In the fifth sentence, add: "and arrhythmia" after "congestive heart failure". After the fifth sentence add: "Large doses of antithyroid drugs (e.g. methimazole or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones". Before the last sentence add: "Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy".

5. DOSAGE AND ADMINISTRATION section:
   Infants and Children
   Table 3:
   After ">12 years" add "but growth and puberty incomplete"
   Replace footnote "A" with "a".