CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-342

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

MOVA Pharmaceutical Corporation
Villa Blanca Industrial Park
State Road No. 1 Km. 34.8
Jose Garrido Avenue (End)
Caguas, P.R. 00725

2. TELEPHONE NUMBER *(Include Area Code)*

(787) 746-8500

3. PRODUCT NAME

Levothyroxine Sodium Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

- [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
- [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

NDA 21-342

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

- [ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*
- [x] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*
- [ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*
- [ ] THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*
- [ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

- [ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- [ ] A CRUDE ALLERGENIC EXTRACT PRODUCT
- [ ] AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- [ ] AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
- [ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
/S/	VP Quality & Regulatory Affairs	4/27/2001

FORM FDA 3397 (5/98)

Faxed by Electronic Document Services/USDHHS (301) 443-2454 EF

1-0378

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS

CONSUMER SAFETY OFFICER LABELING REVIEW

Application Number: NDA 21-342

Name of Drug: Levo-T (Levothyroxine Sodium Tablets, USP)

Sponsor: Mova Pharmaceutical Corporation

Material Reviewed:

Submission Date: April 30, 2001, package insert and 44 bottle labels
February 13, 2002, package insert (revision 1) and 44 bottle labels (same as April 30, 2001)
February 28, 2002 package insert (revision 2) and revised bottle label for 25 mcg x 5000 count

Background and Summary

The firm originally submitted draft labeling (package insert, 44 bottle labels) dated April 30, 2001, that described the storage conditions as follows:

> *Store at controlled room temperature 20° to 25°C (68° to 77°F) with excursions between 15° and 30°C (59° and 86°F). Dispense in a light-resistant container with a child-resistant closure.*

A revised Levothyroxine Sodium Tablets package insert template was faxed to the sponsor on February 8, 2002.

Draft package insert labeling dated February 13, 2002, was submitted by the sponsor.

The chemist determined the word "permitted" should be added to the end of the first sentence of the storage conditions paragraph. The firm was contacted on February 28, 2002, regarding making this change.

On the same day the firm submitted draft labeling dated February 28, 2002, (package insert and a representative label for the 25 mcg x 5000 count bottle) which reflected a minor change in the storage statement requested by FDA. The firm agreed to revise all bottle labels similarly.

Review

The February 28, 2002, draft labeling (package insert for Levo-T was compared with the Levothyroxine sodium template (February 8, 2002). They are identical.

The revised bottle label is acceptable. The additional 43 bottle labels do not contain the requested labeling revision, but the firm agreed to revise the labels exactly like the February 28, 2002, bottle label.

The storage statement will read:

Store at controlled room temperature 20° to 25°C (68° to 77°F) with excursions between 15° and 30°C (59° and 86°F) permitted. Dispense in a light-resistant container with a child-resistant closure.

Conclusions

The draft labeling submitted on February 28, 2002, is acceptable. An approval letter should be drafted.

/S/

Steve McCort
Regulatory Project Manager, HFD-510

Supervisory Comment/Concurrence:

/S/

Enid Galliers
Chief, Project Management Staff, HFD-510

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Drafted: smm/February 28, 2002
Revised/Initialed:
Finalized:
Filename: Document2

CSO LABELING REVIEW

APPEARS THIS WAY
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LEVO-T DRAFT LABELING

DATED FEBRUARY 28, 2002

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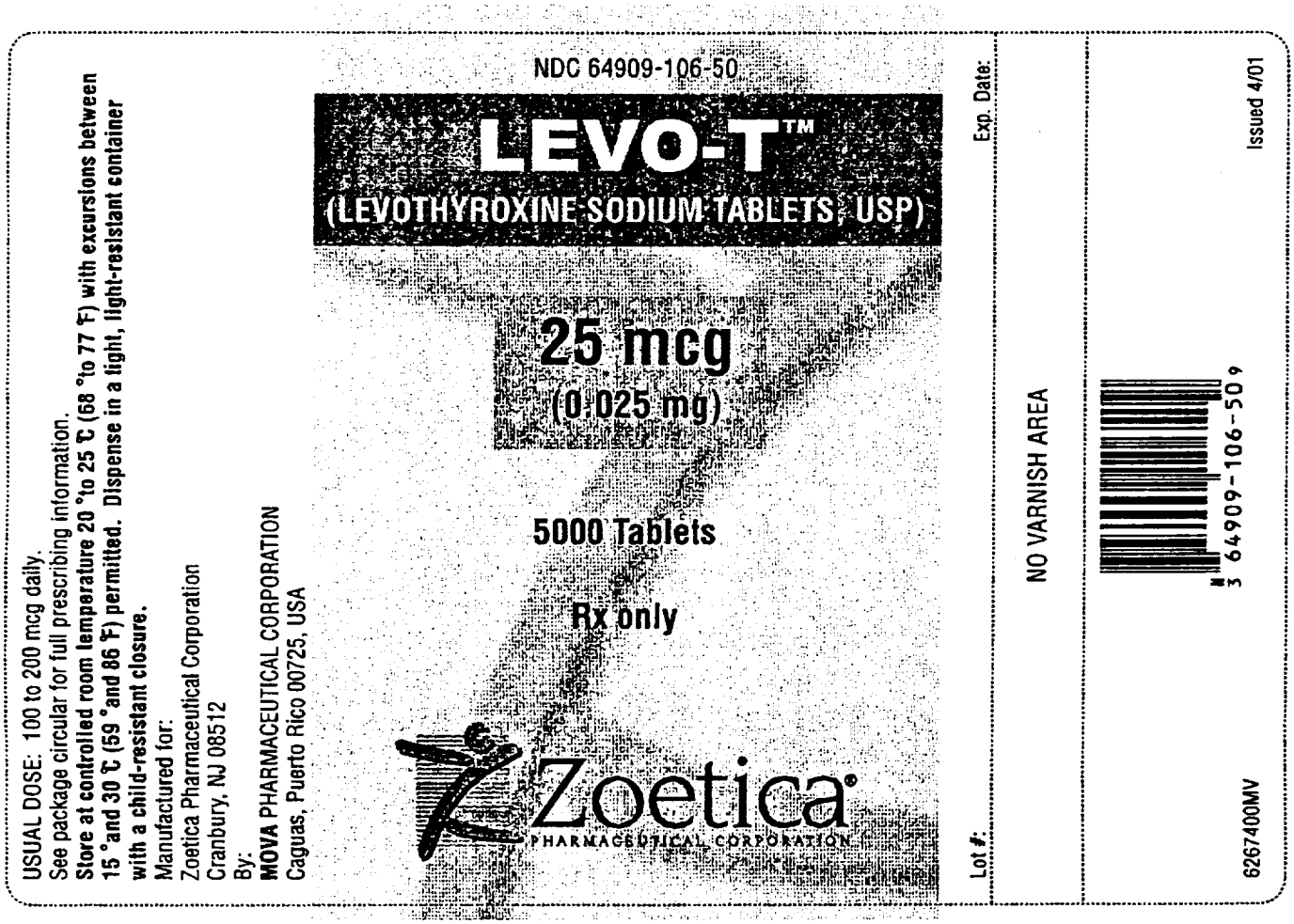
WITHHOLD 18 PAGE (S)

Draft

Labeling

BEST POSSIBLE COPY

SAMPLE LABEL



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

/s/

Stephen McCort
3/1/02 01:21:14 PM
CSO

Enid Galliers
3/1/02 03:55:29 PM
CSO

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EXCLUSIVITY SUMMARY for NDA # 21-342 SUPPL # __

Trade Name Levo-T_ Generic Name Levothroxine Sodium Tablets USP

Applicant Name Mova Pharmaceuticals Corporation HFD- 510

Approval Date MARCH 1, 2002

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 /_x__/ NO /___/

   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.

   _____

   _____

   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 # _____ Drug Name _____

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).

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 /NA/

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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

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 /_x__/ NO /___/ Literature Reports

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:**

This NDA relies on literature reports and the approval of NDA 21-210 and NDA 21-301. It does not contain reports of new clinical investigations or right of reference to such reports.

(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: _____

_____

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(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: _____

_____

_____

_____ _____

Signature of Preparer Date

Title: _____

_____ _____

Signature of Office or Division Director Date

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cc:
Archival NDA ——
HFD-510 /Division File
HFD-510 /RPMS/McCort
HFD-093/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

EXCLUSIVITY SUMMARY for NDA # 21-342 SUPPL # __

Trade Name Levo-T_ Generic Name Levothroxine Sodium Tablets USP

Applicant Name Mova Pharmaceuticals Corporation 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 /_x__/ NO /___/

      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.

      _____

      _____

      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 # _____ Drug Name _____

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 /_x__/ NO /___/

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

NDA # 16-807_____Thyrolar (liatrix) Forest Labs

NDA # 16-680 Euthroid (liotrix) Parke Davis

NDA # 21-210 Unithroid (levothroxine sodium) Jerome Stevens

NDA # 21-301 Levoxyl (levothyroxine sodium) King Pharm

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 /NA/

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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

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 /_x__/ NO /___/ Literature Reports

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 /_x__/

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:**

This NDA relies on literature reports and the approval of NDA 21-210 and NDA 21-301. It does not contain reports of new clinical investigations or right of reference to such reports.

(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

(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.

know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

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ON ORIGINAL

(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: _____

_____

_____

/S/ 2-21-02

Signature of Preparer Date

Title: _____

_____ _____

Signature of Office or Division Director Date

cc:
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HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Mary Parks
3/21/02 03:23:08 PM
For Dr. Orloff

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

DATE RECEIVED: 06/8/01	**DUE DATE:** 08/31/01	**OPDRA CONSULT #:** 01-0113

TO:

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

THROUGH:

Steve McCort
Project Manager
HFD-510

PRODUCT NAME: Levo-T (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:** 21-342	**MANUFACTURER BY:** Mova Pharmaceutical Corporation, Puerto Rico **SPONSOR:** Zoetica Pharmaceutical Corporation, NJ

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 Levo-T to determine the potential for confusion with marketed drug products and pending drug names.

OPDRA RECOMMENDATION: OPDRA has no objection to use of the proprietary name, Levo-T.

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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. 15B032
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 08/15/01

NDA: 21-342

NAME OF DRUG: Levo-T (levothyroxine sodium tablets, USP)

NDA HOLDER: Zoetica Pharmaceutical Corporation, NJ

MANUFACTURER: Mova Pharmaceutical Corporation, Puerto Rico

I. INTRODUCTION

This consult is written in response to a request dated May 2, 2001, from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proposed proprietary name, Levo-T. 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.

PRODUCT INFORMATION

Levo-T (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 product 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 ——— carcinoma of the thyroid.

Levo-T 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 young healthy adults. Elderly patients should be given 1 mcg/kg once a day. The dose of Levo-T in pediatric hypothyroidism will vary with age and body weight. The sponsor proposes supplying Levo-T in child resistant closure bottles of 90, 100, 1000 and 5000 scored color-coded tablets. Levo-T will be available in strengths of 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 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[1,2,3,4] as well as several FDA databases[5] and Thomson & Thomson's SAEGIS™ database[6] for existing drug names for existing drug names which sound alike or look alike to Levo-T 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[7]. 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 Levo-T.

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 [redacted] Levoxyl, [redacted] Levora, Levbid and Luvox as most problematic in terms of the potential for look-alike/sound-alike name confusion. A summary of the identified product is provided in the table below.

DDMAC has no objection to the proposed name Levo-T.

Product Name	Dosage forms & strengths	Usual dose	Observation
Levo-T	Levothyroxine sodium tablets, USP	12.5 to 300 mcg/day per pt response	[redacted]
[redacted]			
Levoxyl	Levothyroxine sodium tablets, USP	12.5 to 300 mcg/day per pt response	*LA/SA
Levatol	Penbutolol sulfate capsules	20 mg qd	*LA/SA
Levora	0.03mg ethinyl estradiol/0.15mg levonorgestrol, tablets	1 tablet daily	*LA/SA
Levbid	L-hyoscyamine sulfate, extended release tablets	0.375 to 0.75 mg q 12 hrs	*LA
Luvox	Fluvoxamine, tablets	100 to 300 mg bid	*LA

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

[1] 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).
[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] Drug Information Handbook 1999-2000, Lacy CF, Armstrong LL, Goldman MP, Lance LL (eds) Lexi-Comp Inc, Hudson
[5] The Established Evaluation System [EES], the Labeling and Nomenclature [LNC] database of proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[6] Data provided by T&T's SAEGIS ™ online service available at www.thomson-thomson.com
[7] 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:

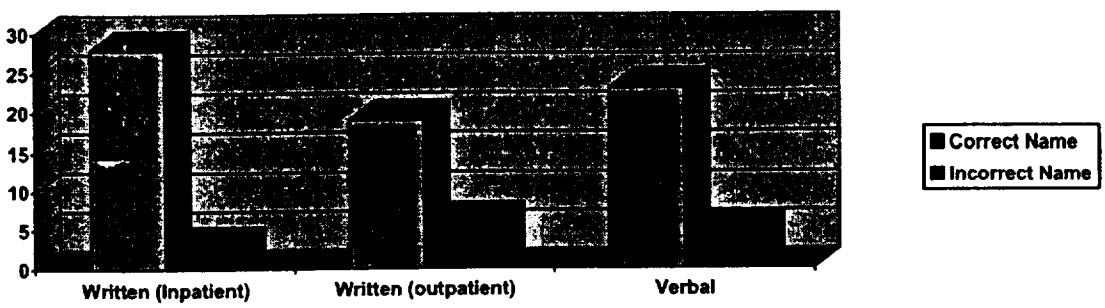
Three studies were conducted by OPDRA involving 116 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between Levo-T and other drug names due to similarity in handwriting and verbal pronunciation. Inpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Levo-T (see below). These prescriptions were scanned into a computer and subsequently delivered to participating healthcare professionals via e-mail. In addition, a verbal prescription order was recorded on voice mail and sent to a sample of the participating healthcare 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 : Levo-T 40 mcg po qd	Verbal RX: Levo-T 40 mcg 1 tab qd
Outpatient RX: LevoT 40 mcg 1 tab qd #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	39	31 (79%)	28 (90%)	3 (10%)
Written Outpatient	38	25 (66%)	19 (76%)	6 (24%)
Verbal	39	28 (72%)	23(82%)	5 (18%)
Total	116	84 (72%)	70 (83%)	14 (17%)



Seventeen-percent of all study participants interpreted the proposed name incorrectly. Five incorrect responses in the verbal study, were phonetic variations of Levo-T (*Levotee* (4), *Levote* (1)). In the written studies 11 participants interpreted the name as Levothyroxine (Written inpatient study 9, Written outpatient study 2). This is expected since Levothyroxine has been marketed under the name Levo-T. Two inaccurate interpretations of the proposed drug name in

the written outpatient study overlapped with existing drug products *Lasix* and *Levoxyl*. Scores of the incorrect responses are summarized in Table II below.

Table II

Incorrectly Interpreted	
Written Inpatient	Lervit
	Levit (2)
Written Outpatient	Lasix*
	Leist (2)
	Lent
	Levoxyl*
	Uvot
Verbal	Levote
	Levotee (4)

*Existing drug products

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name, we were most concerned with the close sound-alike/look-alike qualities between Levo-T and Levatol. We are also concerned that our outpatient written study identified two existing drug products Lasix and Levoxyl.

Levatol is a brand of Penbutolol sulfate, a non-selective beta-adrenergic blocking agent used in the treatment of mild to moderate arterial hypertension. The usual dose of Levatol is 20 mg administered once daily. It is available in 20 mg oral tablets. Although Levo-T and Levotal are both oral tablet dosage forms administered once daily and used for management of chronic disease states, the usual dose of Levo-T is 100 to 200 mcg daily compared to 20 mg for Levatol. Levatol was approved for marketing in the U.S. in January 1989. However, when we used the MedDRA preferred term drug maladministration and search of the Adverse Event Reporting System (AERS) under the drug names Levatol and Levo-T, no report of medication error was identified. Similarly, a search of the DQRS database did not identify any reports of medication error. Although Levatol and Levo-T look and sound alike, the evidence at this time does not support the risk of significant mix-ups.

Lasix is a brand of furosemide, a loop diuretic used in the management edema associated with congestive heart failure, hepatic and renal disease. It is available in 20 mg, 40 mg and 80 mg oral tablets. Oral solutions and injectable dosage forms are also available. Lasix has been on the market since January 1982. However, a search of AERS and DQRS databases failed to identify any reports of medication errors. In addition, the usual dose of Lasix is 20 to 80 mg oral tablets per day while the average dose of Levo-T is 100 to 200 mcg daily. Furthermore these products are used for different indications. The two names may share the first letter "L" but they have distinct phonetic differences. The data available at this time does not indicate that Lasix poses significant risk of sound-alike/look-alike name confusion with Levo-T.

Levoxyl is a brand of levothyroxine sodium. Levoxyl and Levo-T are competitive brands of Levothyroxine Sodium. A search of the AERS revealed no reported cases of medication error between Levo-T and Levoxyl under the MedDRA preferred term drug maladministration.

However, a report from DQRS[8] shows that one patient experienced lack of therapeutic effect after switching from Levo-T to generic Levothyroxine Sodium. Therefore, it is likely that a patient who is stabilized on Levo-T may experience some adverse effect if a different brand of levothyroxine is inadvertently dispensed. Given that Levo-T and Levoxyl have been on the market over a period of time, there is presently no data to show that the two names have been mixed-up due to look-alike and sound alike confusion.

[ ]

Levora (Ethinyl estradiol 0.03 mg/Levonorgestrel 0.15 mg) is a monophasic oral contraceptive. Levo-T and Levora are oral tablets administered once daily, they are usually dispensed in one to three months supply. Both products are used for long term medication therapy and can be prescribe to be used as directed. Although the products do look-alike, the ending sounds "*Tee*" and "*ra*" are different. Moreover, the usual dose of Levora is 1 tablet daily while Levo-T has a usual dose of 100 to 200 mcg daily. Therefore, the likelihood of product mix-ups between Levo-T and Levora appear to be minimal.

Levbid is a brand of L-hyocyamine sulfate extended release tablets. The product is an anticholinergic used to treat gastrointestinal disorders caused by spasms. Levbid is available in 0.375 mg extended release tablets. The suffixes of the names Levobid and Levo-T are distinct in sound ("*bid*" vs "*Tee*"). While Levbid is available in one tablet strength, Levo-T is available in many tablet strengths, therefore dosing strength would be expressed on a prescription script. The usual dose of Levbid is 0.375 to 0.75 mg daily whereas the dose of Levo-T is 100 mcg to 200 mcg daily. There are presently no AERS data to support the risk of product name confusion between Levo-T and Levbid.

Luvox (Fluvoxamine) is serotonine reuptake inhibitor at CNS neurons, indicated for the treatment of major depression and obsessive compulsive disorder. The product is available in 50 mg and 100 mg oral tablets. When poorly scripted the "x"in Luvox could look like a "t" and therefore can be confused with Levot. However, the usual dose of Luvox is 100-300 mg in two divided doses daily, while Levo-T is administered as a 100-200 mcg dose once a day. There is no postmarketing data in AERS supporting any risk of name confusion between Luvox and Levo-T at this time.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

No comments.

[8] WWW location http:/cdernet.cder.fda.gov/dpddcs/FY97_DQRS_REPORTS.PDF

IV. RECOMMENDATIONS

OPDRA has no objection to use of the proprietary name, Levo-T.

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 Sammie Beam at 301-827-3231.

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

Concur:

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

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/s/

David Diwa
9/4/01 04:41:39 PM
PHARMACIST

Jerry Phillips
9/5/01 08:44:16 AM
DIRECTOR

Martin Himmel
9/6/01 12:33:13 PM
MEDICAL OFFICER

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Methods validation of the applcation will be requested.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-342

Mova Pharmaceutical Corporation
Attention: Aracelis Rameriz
Vice President, Regulatory & Quality Affairs
Villa Blanca Industrial Park
State Street Road No. 1 Km/Jose Garrido Avenue (End)
Caquas, P.R. 00725

Dear Ms. Rameriz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levo-T (levothyroxine sodium, USP) Tablets.

We also refer to the dissolution information contained in your April 30, 2001, submission for the NDA.

We have reviewed the referenced material and have the following comments and requests for information:

> Although the Agency was able to set a dissolution tolerance specification for LEVO-T, the results of the dissolution studies indicated a great deal of variability. Please submit a report to the Agency to explain why some of your dissolution data exhibit values that are considerably greater than100%, why two significantly different dissolution values are reported for the same strength on the same day, and why the calibration/standard curve from your Quality Control laboratory did not appear linear.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

David Orloff
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-342

Mova Pharmaceutical Corporation
Attention: Arecelis Ramirez
Vice President, Regulatory and Quality Affairs
Villa Blanca Industrial Park
State Street Road No. 1 Km 34.8/Jose Garrido Avenue (End)
Caquas, P.R. 00725

Dear Ms. Ramirez:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Levo-T (Levothyroxine Sodium Tablets, USP) 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg strengths.
Review Priority Classification:	Standard (S)
Date of Application:	April 30, 2001
Date of Receipt:	May 1, 2001
Our Reference Number:	NDA 21-342

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 30, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 1, 2002, and the secondary user fee goal date will be May 1, 2002.

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

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

Steve McCort
Regulatory Project Manager
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Stephen McCort
5/17/01 11:34:23 AM

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No safety update was needed for this application.

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

NDA Number:	021342	**Trade Name:**	LEVO - T(LEVOTHYROXINE SODIUM)TABLETS
Supplement Number:	000	**Generic Name:**	LEVOTHYROXINE SODIUM
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	HYPOTHYROIDISM/ PITUITARY/TSH/ SUPPRESSION
Original NDA Action Date:	5/1/01		

Indication # 1 Treatment of hypothyroidism and pituitary TSH supression

Comments (if any): Recommend approval of application.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 years	18 years	Completed	

Comments: The need for stuides was satisfied since the sponsor cited relevant stuides from the literature that addressed the pediatric population

This page was last edited on 2/25/02

Signature /S/ 2-25-02 Date

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