CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-342

CHEMISTRY REVIEW(S)

NDA 21-342

Levo-T™ (levothyroxine sodium tablets, USP)

MOVA Pharmaceutical Corporation

David B. Lewis, Ph.D.

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

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 21-342

2. REVIEW #: 1

3. REVIEW DATE: 08/02/02

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND ——	28/11/97

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL NDA	30/04/01
AMENDMENT[1]	21/05/01
AMENDMENT[2]	26/10/01
AMENDMENT[3]	24/01/02
AMENDMENT[4]	04/02/02
AMENDMENT[5]	08/02/02

1. Provides a written agreement to manufacture additional lots and perform dual testing for potency assay per FDA request.
2. Provides updated stability data.
3. Provides updated stability data
4. Provides representative COA's for excipients
5. Provides an agreement to establish an in-process specification and clarifies the 21 CFR citation for EA categorical exclusion.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	MOVA Pharmaceutical Corporation
Address:	Villa Blanco Industrial Park, State Road No. 1, Km 34.8 Jose Garrido Avenue [end] Caguas, Puerto Rico 00725
Representative:	Aracelis M. Ramírez
Telephone:	(787) 746-8500 X 1149 (Phone) (787) 745-1750 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Levo-T™
b) Non-Proprietary Name (USAN): levothyroxine sodium tablets, USP
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(2); The RLD is Unithroid® (levothyroxine sodium tablets, USP), manufactured by Jerome Stevens Pharmaceuticals, Bohemia, NY (NDA 21-210).

10. PHARMACOL. CATEGORY: Thyroid

11. DOSAGE FORM: Tablets (immediate release)

12. STRENGTH/POTENCY:

25, 50, 75, 88, 100, 112, 125, — 150, 175, 200, and 300 mcg per tablet.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

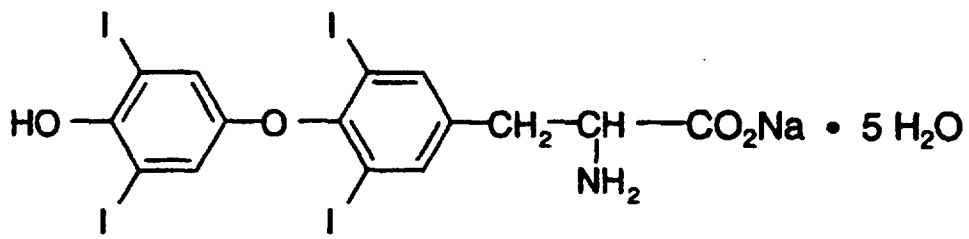
Established, INN, USAN Name: Levothyroxine sodium, USP

Inverted IUPAC name: L-Tyrosine, *O*-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt, hydrate.

Molecular formula: $C_{15}H_{10}I_4NNaO_4 \bullet xH_2O$

Molecular Weight: 798.85 g/mol (anhydrous)

Structure:



APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Levothyroxine sodium, USP	3	Adequate	October 11th, 2001	
[redacted]	III	[redacted]	[redacted]	3	Adequate	May 10th, 1999	
[redacted]	III	[redacted]	[redacted]	3	Adequate	July 13th, 1999	
[redacted]	III	[redacted]	[redacted]	3	Adequate	June 23rd, 2000	
[redacted]	III	[redacted]	[redacted]	3	Adequate	August 25th, 1998	
[redacted]	III	[redacted]	[redacted]	3	Adequate	August 12th, 1999	
[redacted]	III	[redacted]	[redacted]	3	Adequate	September 1st, 1999	
[redacted]	III	[redacted]	[redacted]	3	Adequate	October 8th, 1993	Meets the requirements of 21 CFR 177.1520, 178.3297, and 178.2010
[redacted]	III	[redacted]	[redacted]	3	Adequate	July 27th, 2000	
[redacted]	III	[redacted]	[redacted]	3	Adequate	July 28th, 1999	
[redacted]	III	[redacted]	[redacted]	7	N/A	N/A	Meets the requirements of 21 CFR 177.1520
[redacted]	III	[redacted]	[redacted]	3	Adequate	September 3rd, 1997	
[redacted]	III	[redacted]	[redacted]	3	Adequate	May 3rd, 1999	

Chemistry Review Data Sheet

[redacted]	III	[redacted]	3	Adequate	October 12th, 2000	
[redacted]	III	[redacted]	1	Adequate	January 15th, 2002	
[redacted]	III	[redacted]	3	Adequate	May 18th, 2001	

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

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

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	22/05/01	N/A
Pharm/Tox	Acceptable	21/06/01	Karen Davis-Bruno, Ph.D.
Biopharm	Approvable (pending)	pending	Steve Johnson, Pharm. D.
LNC			
Methods Validation	Pending		
OPDRA (now ODS)	Acceptable	15/08/01	David Diwa, Pharm. D.
EA	Categorical Exclusion	Original application	
Microbiology			

The Chemistry Review for NDA 21-342

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: From the standpoint of chemistry, this application can be **approved.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: The following Phase 4 Commitment is recommended:

- The applicant agreed to establish an in-process specification for levothyroxine sodium assay for the ——— stage within one year of approval.

II. Summary of Chemistry Assessments

The drug product Levo-T™ (levothyroxine sodium tablets, USP) has been marketed by MOVA Pharmaceutical Corporation for several years without an approved NDA. This application was filed in response to the FR notice dated August 14th, 1997, which declared that drug products containing levothyroxine sodium were considered to be new drugs, and were subject to NDA review by the Agency. The drug product proposed in this NDA represents a reformulation (the previously marketed MOVA product contained a stability overage; the proposed NDA drug product is targeted to 100 % label claim at release). The application is a 505(b)(2) NDA, which refers to Unithroid® (levothyroxine sodium tablets, USP); NDA 21-210 (Jerome Stevens, Bohemia N.Y.) as the reference listed drug (first approved levothyroxine sodium NDA).

A. Description of the Drug Product(s) and Drug Substance(s): Levo-T™ (levothyroxine sodium tablets, USP) is an immediate-release solid oral tablet, which is proposed for marketing in eleven strengths ranging from 25 to 300 mcg per tablet. The drug product formulation contains the following inactive ingredients: —— and microcrystalline cellulose ———, sodium starch glycolate ——— magnesium stearate ———, and various FD&C (or D&C) aluminum lake dyes (colorants). All tablet strengths are the same size (*ca.* —mg per tablet); the various strengths are differentiated by color and debossing. The manufacturing process for the drug product involves ——— ——— Levo-T™ tablets are packaged in HDPE bottles (90/100-, 1000-, and 5000-count containers). Levothyroxine sodium tablets are compendial (current USP monograph), but the

sponsor utilized a combination of USP monograph analytical methods and in-house analytical methods to test the product at release and during stability. A bracketed (reduced) stability design was utilized, in which the 25-, 100-, and 300-mcg tablets were stability tested (total of eight lots) and the stability of the other nine tablet strengths was interpolated based on the data from the three tested strengths. The drug substance, levothyroxine sodium, USP, is manufactured by ——— The drug product manufacturer refers to DMF — for CMC information regarding the drug substance. DMF — has been reviewed several times in support of NDA's for levothyroxine sodium tablets. The most recent review, dated October 11th, 2001 (D. Lewis, Ph.D., reviewer) found DMF — adequate to support all of the NDA's for levothyroxine sodium tablets currently on file with the Agency (including this NDA).

The primary focus of this CMC review is the demonstration of the sponsor's ability to manufacture a stable drug product without the use of excess drug substance (stability overage). *Special attention was paid to the analytical method for potency assay, in order to verify that all of the primary stability lots were actually released without overage.* This evaluation involved the review of two different analytical methods for potency assay, along with test results for primary stability studies and test results for release and stability of a second group of Levo-T™ lots. The two different analytical assay methods were reviewed in order to evaluate whether several release values represented a stability overage, or an artifact of the analytical method used for analysis. The draft labeling was submitted to ODS (formerly OPDRA) for consult review. Issues of dissolution and bioavailability were addressed in the Biopharmaceutics Review.

B. Description of How the Drug Product is Intended to be Used: The drug product is intended for market in the following strengths: 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg per tablet. Usual dosing is once daily, with typical daily doses ranging from 12.5 to 200 mcg per day (doses greater than 200 mcg daily are rarely required). The drug product is supplied in 90-, 100-, 1000-, and 5000-count bottles, with the larger sizes intended for distribution to pharmacies (bulk packaging), and the smaller sizes intended for pharmacy labeling and dispensation directly to patients (in the original package). The long-term ICH stability data submitted for this NDA support an expiry of 18 months at this time with storage at room temperature (25°C, 77°F).

C. Basis for Approvability or Not-Approval Recommendation: This NDA is recommended for approval from the standpoint of chemistry, manufacturing and controls.

III. Administrative

A. Reviewer's Signature

David B. Lewis, Ph.D., reviewer

B. Endorsement Block

C. CC Block:

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/

David Lewis
2/20/02 01:06:11 PM
CHEMIST
Adequate information has been provided regarding CMC. From the standpoint of chemistry, this application can be approved.

Need an electronic signature

Sheldon Markofsky
2/21/02 08:18:02 AM
CHEMIST

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Attached ESTABLISHMENT EVALUATION REPORT

Application: NDA 21342/000
Priority: 5S
Org Code: 510
Stamp: 01-MAY-2001 Regulatory Due: 01-MAR-2002
Action Goal:
District Goal: 31-DEC-2001
Applicant: MOVA PHARMS
STATE RD 1KM 348 JOSE GARRIDO /
CAGUAS, PR 00725
Brand Name: LEVOE-T(LEVOTHYROXINE SODIUM)TABLETS
Established Name:
Generic Name: LEVOTHYROXINE SODIUM
Dosage Form: TAB (TABLET)
Strength: 25 - 300 MCG

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

Overall Recommendation:

ACCEPTABLE on 22-MAY-2001 by EGASM

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

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAY-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-MAY-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment: 2650178
MOVA PHARMACEUTICALS CORP
CARR 1 KM 34.9 CALLE ZAFIRO URB
CAGUAS, PR 00725
DMF No:
AADA No:

Profile: TCM
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-MAY-2001
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE: 5-16-01
I spoke with Ms. Ramirez regarding the ——— cited as the source of the apparent overages seen for the 25-mcg tablets. I requested that MOVA manufacture three additional lots of 25-mcg tablets, perform dual assays at release (STM 771-013, revisions 6 and 7), record the variability, and place these lots on stability. Ms. Ramirez told me that MOVA has already planned to do this. They have scheduled a June 1 manufacture of nine additional lots of drug product (3 apiece of 25 and 300-mcg tablets, 2 of 100-mcg tablets, and 1 of 50-mcg tablets). They will place all of these lots on full stability, and will perform dual assay testing (STM 771-013, Revisions 6 and 7). I told Ms. Ramirez that if MOVA could assay retained samples of 75, 88, 112, 150, and 175-mcg tablets (STM 771-013, revisions 6 and 7) and duplicate the variability seen for the 100-mcg tablets, this would be valuable confirmatory evidence towards validated their claim of strength-related assay bias. She said that they would probably do this. validating	**NDA NUMBER: 21-342** **PRODUCT NAME: Levo-T** (Levothyroxine sodium tablets, USP) **FIRM NAME: MOVA Pharmaceutical Corporation** **NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:** Aracelis Ramirez, Quality and Regulatory Affairs VP **TELEPHONE NUMBER:** (787) 746-8500 X 1149
SIGNATURE:	**DIVISION:** DMEDP

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE: February 8th, 2002
	NDA NUMBER: 21-342
I requested the following items regarding NDA 21-342: 1) The 21 CFR reference regarding categorical exclusion from EA should be corrected, from 25.5 (a) to 25.31 (b) and/or (c). 2) The firm should agree to establish an in-process specification for levothyroxine content in the [redacted]. The specified range is to be determined by the firm, and the in-process specification should be established within one year.	PRODUCT NAME: Levo-T™ (levothyroxine sodium tablets, USP)
Ms. Juárez agreed to these requests. A Facsimile copy of this information will be sent today (2-8-2), to be followed by an official amendment (submitted to the NDA file).	FIRM NAME: MOVA Pharmaceutical Corporation
APPEARS THIS WAY ON ORIGINAL	NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Marla Juárez, Regulatory Affairs and Compliance
	TELEPHONE NUMBER: (787) 746-8500 (X 1108)
SIGNATURE:	DIVISION: DMEDP

APPEARS THIS WAY
ON ORIGINAL

OPDRA Consult: Pages 2-6 of the OPDRA consult address the method by which the proposed proprietary name was evaluated for look-alike names and sound-alike names; these pages were not scanned into the review. The two sections of the consult which were reproduced and scanned into the review were the cover sheet (page 1) and the recommendations (page 7).

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.

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

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.

/S/

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