

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-116

CHEMISTRY REVIEW(S)

10.21.02



NDA 21-116

Thyro-Tabs® (levothyroxine sodium tablets, USP)

Lloyd, Inc.

David B. Lewis, Ph.D.

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



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Chemistry Review Data Sheet

1. NDA 21-116
2. REVIEW #: 2
3. REVIEW DATE: October 21st, 2002
4. REVIEWER: David B. Lewis, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL NDA	19/08/99
CMC REVIEW NO. 1	12/06/00
APPROVABLE (AE) LETTER	20/06/00

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
AMENDMENT	22/04/02
AMENDMENT	27/05/02
AMENDMENT	05/09/02
AMENDMENT	25/09/02
FAX	04/10/02
FAX	21/10/02

- The amendment dated April 22nd, 2002 provides responses to the approvable (AE) letter dated June 20th, 2000.
- The amendment dated May 27th, 2002 provides draft labeling for the drug product.
- The amendment dated September 5th, 2002 provides updated (12 month) stability data for the re-formulated batches.
- The amendment dated September 25th, 2002 provides supportive stability data for the original formulation.



Chemistry Review Data Sheet

- The FAX transmission dated October 4th, 2002 provides the requested expiration dating periods for all strengths of Thyro-tabs.
- The FAX transmission dated October 21st, 2002 provides a revised storage statement.

7. NAME & ADDRESS OF APPLICANT:

Name: Lloyd, Inc.
Address: 604 West Thomas Ave., Shenandoah, Iowa 51601-0130
Representative: Dr. Joseph W. Denhart, VP Regulatory Affairs
Telephone: (712) 246-4000 (phone); (712) 246-5245 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Thyro-Tabs®
- 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 Listed Drug (LD) is Unithroid® (levothyroxine sodium tablets, USP), manufactured by Jerome Stevens (Bohemia, NY). Unithroid® is marketed as 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300-mcg tablets, and is filed under NDA 21-210.

10. PHARMACOL. CATEGORY: Thyroid

11. DOSAGE FORM: Immediate-release tablets

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

13. ROUTE OF ADMINISTRATION: Oral



Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]: SPOTS product – Form Completed Not a SPOTS product

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

- Established name (USAN/INN): **Levothyroxine sodium**
- Inverted IUPAC Name: **L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3',5'-diiodo-, monosodium salt, hydrate.**
- Molecular formula: **C₁₅H₁₀I₄NNaO₄•5H₂O**
- Molecular weight(s): **888.96 g/mol (pentahydrate) and 798.86 g/mol (anhydrous material).**
- The chemical structure is as follows:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II	f	Levothyroxine sodium, USP	3	Adequate	11/10/01	



Chemistry Review Data Sheet

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	[pending]		
Pharm/Tox	Approval	24/05/00	R. Steigerwalt, Ph.D.
Biopharm	Approval	19/11/01	S. Johnson, Pharm.D.
LNC	N/A		
Methods Validation			
OPDRA	Acceptable	12/06/00	
EA	Acceptable	12/06/00	D. Lewis, Ph.D.
Microbiology	N/A		



The Chemistry Review for NDA 21-116

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval, pending acceptable EES report

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

None

II. Summary of Chemistry Assessments

NDA 21-116 was originally submitted to the Agency on August 19th, 1999. Chemistry, manufacturing and controls (CMC) review No. 1, dated June 8th, 2000 resulted in an approvable (AE) letter being communicated to the sponsor. *The major deficiency noted in the original application was a poor stability profile for the 25-mcg tablets.* The firm developed a revised manufacturing process and re-submitted the application along with 9 months of accumulated long-term and intermediate ICH stability data; this data was amended to include 12-month test results during the review cycle. The manufacturing changes covered ALL strengths of the drug product; thus stability data was submitted in support of the entire strength range. Other CMC-related changes included the addition of two new tablet strengths (88 and 112-mcg) and revised analytical methods for potency assay and dissolution.

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

The drug product, Thyro-tabs® (levothyroxine sodium tablets, USP) is a "caplet-shaped" color-coded potency marked tablet. The product is intended for marketing in eleven (11) strengths, ranging from 25 to 300 mcg per tablet. The product is packaged in 100-count and 1000-count bottles. Thyro-tabs are manufactured via _____ of excipients and the active ingredient; the excipients used in the drug product are microcrystalline cellulose, NF; calcium phosphate dibasic•2H₂O, USP; magnesium stearate, NF; povidone, USP; and various FD&C or D&C aluminum lake colorants. The tablet weight is 120 mg, and the drug substance makes up _____ of the tablet weight. Stability data for the drug product was accumulated using a reduced design "stability bracket", in which the 25, 50, 100, and 300-mcg tablets were stability tested and the tentative expiry for the other seven tablet strengths were estimated based on the data for the representative tested bracket strengths. Stability testing was done for the 100-count bottles only per FDA recommendation, since the 100-count package presentation represents a

Executive Summary Section

worse-case scenario regarding stability than the 1000-count package. The 25- and 50-mcg tablets were stability-tested at 2-8°C (refrigerator), 25°C/60% RH (ICH long-term storage) and 30°C/60% RH (ICH intermediate storage). The 100- and 300-mcg tablets were stability tested at 25/60 and 30/60 only. During the review cycle, the stability data was updated to 12 months (all storage conditions). Statistical analyses were performed for all primary stability studies (all 4 tested strengths in all storage conditions).

The drug substance, levothyroxine sodium, USP (T₄) is manufactured and supplied by Bulk T₄ complies with the requirements of the current USP monograph, and is also tested for particle size and degradation products and/or process impurities. Chemistry, manufacturing and controls (CMC) information regarding T₄ is contained in the Type II DMF, which has been reviewed several times in support of levothyroxine sodium tablet NDA's. The most recent review, dated October 11th, 2001 (D. Lewis, Ph.D., reviewer), found DMF adequate to support NDA's for levothyroxine sodium tablets.

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

The drug product is intended for use in treating hypothyroidism and a variety of euthyroid goiters. The recommended (typical) daily dose ranges from 12.5 to 200 mcg, and is usually administered once daily. Thyro-tabs® are proposed for marketing in eleven (11) strengths: 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg per tablet. The proposed expiration dating period is for the 25-mcg tablets, for the 50, 75, and 88-mcg tablets, and for the 100, 112, 125, 150, 175, 200, and 300-mcg tablets with storage at 25°C (excursions permitted between 15 and 30°C). The proposed shelf life is acceptable, and is supported by 12 months of primary stability data accumulated at 2-8°C, 25°C/60% RH, and 30°C/60% RH, statistical analysis of the stability data (Lower-sided 95% confidence level) and 36 months of supportive stability data accumulated on the original NDA primary lots.

C. Basis for Approvability or Not-Approval Recommendation

The product is recommended for approval pending the results of the cGMP inspection. Satisfactory responses to the deficiencies outlined in the AE letter dated June 20th, 2000 have been provided.

III. Administrative

A. Reviewer's Signature : DFS

B. Endorsement Block

C. CC Block

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/s/

David Lewis

10/21/02 11:28:18 AM

CHEMIST

From the standpoint of chemistry, the application may be approved pending an acceptable cGMP report from the Office of Compliance.

See pages 5 & 6 (SUBMISSIONS BEING REVIEWED) and 51-53 (LABELING, regarding the storage statement).

Duu-gong Wu

10/21/02 06:06:44 PM

CHEMIST

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21116/000
Org Code : 510
Priority : 5S

Sponsor: LLOYD
604 WEST THOMAS AVE
SHENANDOAH, IA 51601

Stamp Date : 20-AUG-1999
PDUFA Date : 24-OCT-2002
Action Goal :
District Goal: 25-AUG-2002

Brand Name : THYRO TABS (LEVOTHYROXINE
SODIUM TABLETS)
Etab. Name:
Generic Name: LEVOTHYROXINE SODIUM TABLETS
Dosage Form: (TABLET)
Strength : 25 - 300 MCG

FDA Contacts: S. MCCORT
D. LEWIS
D. WU

Project Manager (HFD-510) 301-827-6415
Review Chemist (HFD-510) 301-827-6420
Team Leader (HFD-510) 301-827-6375

Overall Recommendation:

ACCEPTABLE on 22-OCT-2002 by S. FERGUSON (HFD-324) 301-827-
0062

WITHHOLD on 20-SEP-2002 by B. HARTMAN (HFD-324) 301-827-0067

ACCEPTABLE on 13-JUN-2000 by J. D AMBROGIO (HFD-324) 301-827-
0062

Establishment : CFN : FEI : 3002806523

DMF No: AADA:

Responsibilities:

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-SEP-99
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : 1942094

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 14-OCT-99
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : — FEI : 1927976

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-SEP-99
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1911196 FEI : 1911196

LLOYD INC
907 5TH AVE
SHENANDOAH, IA 51601

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-OCT-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

/s/

David Lewis

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CHEMIST

The cGMP status for NDA 21-116 is ACCEPTABLE (dated
10-22-02). An action may be taken (approval).

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

NDA #: 21-116

DATE REVIEWED: 6-12-00

REVIEW #: 1

REVIEWER: David B. Lewis, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	08-19-99	08-20-99	08-26-99
AMENDMENT	01-12-00	01-28-00	
AMENDMENT	01-29-00	01-31-00	
AMENDMENT	02-03-00	02-07-00	
AMENDMENT	03-08-00	03-10-00	
AMENDMENT	04-05-00	04-10-00	
AMENDMENT	04-20-00	04-21-00	

NAME & ADDRESS OF APPLICANT:

Lloyd, Inc. of Iowa
604 West Thomas
Shenandoah, Iowa
51601-0130
(712) 246-4000 (Phone)
(712) 246-5245 (FAX)

DRUG PRODUCT NAME

Proprietary:

Thyro-Tabs®

Established:

Levothyroxine Sodium Tablets, USP

Code Name/#:

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION:

Treatment of hypothyroidism, thyroid goiter, and thyroid cancer

DOSAGE FORM: Solid Oral tablets

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

ROUTE OF ADMINISTRATION: Oral

Rx/OTC:

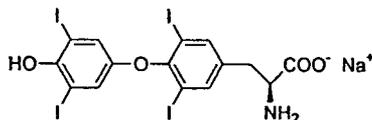
Rx OTC

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

Levothyroxine Sodium, USP

$C_{15}H_{10}NI_4O_4Na \cdot xH_2O$

798 g/mol



SUPPORTING DOCUMENTS: Letters of Authorization, allowing reference to the following DMF's:

RELATED DOCUMENTS (if applicable):

Type/Number	Subject	Holder	Status	Review Date
DMF — Type I	Levothyroxine sodium	—	Acceptable	4-29-99
DMF — Type II			N/A	N/A
DMF — Type II			N/A	N/A
DMF — Type III			Adequate	5-07-99
DMF — Type II			N/A	N/A
DMF — Type II			N/A	N/A
DMF — Type III			Adequate	11-07-94
DMF — Type III			Adequate	5-11-99

CONSULTS: OPDRA

REMARKS: Lloyd, Inc. (Shenandoah, Iowa) is submitting NDA 21-116 in accordance with the Federal Register Notice of August 14th, 1997 (Volume 62, Number 157), in which drug products containing levothyroxine sodium were re-classified as new drugs, and were subject to formal NDA application and FDA review. The applicant is currently marketing the levothyroxine sodium drug product for animal use. The application is being reviewed by DMEDP (HFD-510) as a 505(b)(2) New Drug Application. The drug substance is manufactured and supplied by _____ and the applicant referred to DMF — for CMC information on the drug substance. DMF — has been reviewed previously, and found adequate to support an NDA submission (see Chemistry Reviews 1 and 2, dated 3-16-98 and 4-29-99, respectively; D. Lewis, Ph.D., reviewer). The amendment dated 12-30-99 provides a request for a Teleconference (concerning the future qualification of an alternate source of drug substance. The amendment dated 1-12-00 provides a revised specification for tablet dissolution. The amendments dated 1-29-00, 2-03-00, 3-08-00, and 4-20-00 all provide updated stability data, with the 4-20-00 amendment containing a 12-month summary of all accumulated stability data. **The amendment dated 4-05-00 provides a revised formulation section, indicating a — manufacturing overage (which is the actual formulation used to manufacture the stability lots).** The stability submission was in the form of a reduced stability design (stability bracket), in which data for lots of the 25, 100, and 300-mcg tablet strengths were used to evaluate the stability for all strengths of the drug product. The submitted (bracketed) stability data supports the stability of the 100- through 300-mcg tablet strengths for up to 12 months, but not the 25, 50, and 75-mcg strengths, due to the stability failure of the 25-mcg tablets, which represent the lowest extreme in the stability bracket. The firm should be given a choice of withdrawing the lower three strengths (25, 50, and 75mcg tablets), and receiving an approval for the 100, 125, 150, 175, 200, and 300-mcg tablets. An EER was submitted to the Office of Compliance (OC) on 9-27-99 via EES. The requisite inspections have been completed, and the official OC results are pending (as of 6-08-00). The labeling was consulted to OPDRA for review (trade-name and labeling text); OPDRA had neither objections to the use of the trade-name Thyrotabs, nor any significant comments, regarding the labeling and packaging.

CONCLUSIONS & RECOMMENDATIONS: regarding chemistry, manufacturing and controls, the application is approvable, pending a satisfactory response to the information requests delineated in the Draft List of Information requests.

cc:

Org.

HFD-510/Division File

HFD-820/Chemist/D. Lewis/DG Wu

HFD-510/S. McCort

151

R/D Init by:

151
v

David B. Lewis, Ph.D.
Review Chemist

Filename: NDA 21-116 Review

26 Page(s) Withheld

MCCORT

DEC 18 1998

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

IND # 57,315

Division: HFD-510

Chemistry Review #: 1

Date Completed: 12-18-98

Applicant:

Lloyd, Incorporated

Address:

P.O. Box 130
604 West Thomas Ave.
Shenandoah, Iowa 51601-0130
(712) 246-4000 (Phone)
(712) 246-5245
W.E. Lloyd, D.V.M., Ph.D. (CEO)

Product Name(s):

Thyro-Cap™

Proprietary:

Levothyroxine sodium tablets, USP

Non-proprietary:

Compendium:

USAN:

Dosage Form(s) and Route(s) of Administration:

Oral 50 µg, 100 µg, and 300 µg tablets

Pharmacological Category and/or Principal Indication:

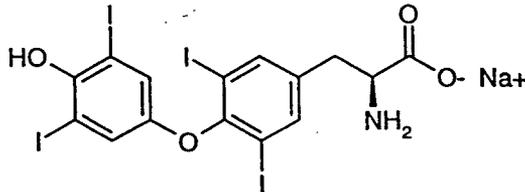
Thyroid principle/replacement of endogenous thyroxin in hypothyroid patients

Structural Formula and Chemical Name:

O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosine monosodium salt

C₁₅H₁₀I₄NNaO₄

Molecular Weight = 798.86



Initial Submission:

11-20-98

Related Documents:

DMF's

Supporting Documents:

Letter of authorization to refer to DMF

dated 11-05-98; LOA to refer to DMF

, dated 11-17-98; LOA to refer to

dated 11-

06-98; LOA to refer to DMF

, dated 11-17-98; LOA to refer to DMF

, dated 11-17-98; LOA to refer to DMF

, dated 11-17-

98; LOA to refer to DMF

, dated 11-12-98.

Remarks/Comments: Lloyd, Inc. is submitting under 21 CFR 312.20 this IND (57,315) for levothyroxine sodium. This application has been submitted pursuant to the Federal register Notice [FR 62(157), pp. 43535-43438], in which the FDA has ruled that drug products containing levothyroxine sodium are considered to be "new drugs". Lloyd, Inc. (Shenandoah, Iowa) has been manufacturing levothyroxine tablets for 16 years for veterinary use. Lloyd currently manufactures levothyroxine under GMP conditions for veterinary use in eight dose strengths ranging from 100 mg to 800 mg; approximately — batches (usually — tablets per batch) have been manufactured since 1982. The firm has re-formulated the drug product for human use. The investigational drug product has the provisional trademark — but is actually a "caplet-shaped tablet". The tablet strengths provided for in IND 57,315 are 50 µg, 100 µg, and 300 µg, and the products are formulated with a — manufacturing overage (of levothyroxine). It is not known if this overage is maintained in the finished drug product. The drug substance is supplied by — CMC information regarding this material is provided in DMF —. A Letter of Authorization, allowing reference to DMF — dated 11-05-98 is included. The application includes drug product components & composition; acceptance criteria for all materials; a manufacturing flow-chart and quantitative batch compositions. In-process controls are included. A description of the container/closure system is provided, along with references to pertinent Type III packaging DMF's. The finished product specifications are similar to the requirements of the current USP monograph for levothyroxine sodium tablets with two exceptions (tighter assay specifications for the Lloyd, Inc. product; and the absence of a specific identity test for levothyroxine sodium for the Lloyd product). A stability protocol is provided; there is no completed stability data provided in the submission. Historical stability data is provided for the veterinary product, as supporting information. There are no blank or executed batch records included in this IND submission.

Conclusion and Recommendation: This application is adequate to support IND studies, regarding chemistry, manufacturing and controls information. See Draft Letter of deficiencies/ request for further information to be forwarded to the sponsor, regarding subsequent NDA submission.

cc: IND Orig.
HFD-510
HFD-510/D Lewis/CSO
HFD-510/DG Wu/
R/D initialed by

151
12-18-98
David Lewis, Ph.D.
Review Chemist

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