
INTRA-DIVISION MEMORANDUM

TO: STEPHEN MCCORT
FROM: STEVEN B. JOHNSON
SUBJECT: NDA 21-116 AMENDMENT #22 – USP DISSOLUTION TOLERANCE SPECIFICATION
DATE: 10/10/02
CC: HAE-YOUNG AHN, ENID GALLIERS, AND LARRY OUDERKIRK

Stephen,

Given the new single and multipoint dissolution information submitted in NDA 21-116 N-022 on 4-OCT-2002, the Office of Clinical Pharmacology and Biopharmaceutics agrees with the sponsor that the dissolution method and tolerance specifications for THYRO-TABS brand of levothyroxine sodium tablets are listed in the table below. Please convey this information to the sponsor at your earliest convenience.

Apparatus Type	USP # 2 (paddles)
Media	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume	500 mL
Speed of Rotation	50 RPM
Tolerance Specifications	NLT — (Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes

Thank you,

Steven B. Johnson, Pharm.D.
CPB Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader

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

/s/

Steve Johnson
10/10/02 07:44:16 AM
BIOPHARMACEUTICS

Hae-Young Ahn
10/10/02 09:13:36 AM
BIOPHARMACEUTICS

21 Page(s) Withheld

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

DATE RECEIVED: 5/30/00

DUE DATE: 6/10/00

OPDRA CONSULT #: 00-0156

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

THROUGH:
Steve McCort
Project Manager
HFD-510

PRODUCT NAME:
Thyro-Tabs
(levothyroxine sodium tablets,
USP)
NDA #: 21-116

MANUFACTURER: Lloyd Inc.

SAFETY EVALUATOR: Peter Tam, RPh.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Thyrotab (without hyphen). See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW

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 names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

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

(acting)
Peter Tonig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

6/7/00

07/28/2004 13:02 FAX 3014439282

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 6/5/00
NDA#: 21-116
NAME OF DRUG: Thyro-Tabs (levothyroxine sodium tablets, USP)
NDA HOLDER: Lloyd Inc.

I. INTRODUCTION:

This consult is in response to a 5/30/00 request by the Division of Metabolic and Endocrine Drug Products to review the proposed proprietary name, Thyro-Tabs, regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Thyro-Tabs (levothyroxine sodium tablets, USP) tablets contain synthetic crystalline tetraiodothyronine sodium salts. Synthetic levothyroxine sodium is identical to that produced in the human thyroid gland.

The normal thyroid gland contains approximately 200 mcg T₄ per gram of gland and 15 mcg of T₃ per gram. Only a small portion of T₃ is produced by the thyroid gland. A majority (about 80%) of T₃ comes from the metabolism of T₄ by monodeiodination of the outer ring. Therefore, when thyroxine (T₄) is given to hypothyroid patients in doses that produce normal concentrations of T₄, the plasma concentration of T₃ also normalizes.

Oral absorption of levo-thyroxine ranges from 50-80 percent of the administered dose. Absorption is slightly increased when the drug is taken on an empty stomach with no significant clinical relevance and decreased when taken with aluminum-containing antacids, sucralfate, iron, and bile acid sequestrants.

T₄ has a plasma half-life of 6 to 7 days and T₃ has a plasma half-life of 1 to 2 days. The liver is the major site of metabolism for both hormones and is excreted in the bile. Thyro-Tabs is indicated for replacement therapy or supplemental therapy in patients with diminished or absent thyroid function.

Thyro-Tabs will be supplied in tablets of 25 mcg, 50 mcg, 75 mcg, 100 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg, in bottles of 100 and 1000.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound alike or look alike to Thyro-Tabs 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 was also conducted⁵. 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 (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

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).

1. The panel discussed the following sound-alike and look-alike drug names:

Product Name	Dosage form(s), Generic name	Usual Dose	Observation
Thyro-Tabs	Tablets, levothyroxine 25, 50, 75, 100, 125, 150, 175, 200, 300 mcg	Dosage and rate of administration is individualized and should be confirmed by lab tests.	
Thyrolar	Tablets, a uniform mixture of T ₄ and T ₃ in a 4 to 1 ratio by weight	60-120 mg/day	*SA/LA

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

The panel concluded that the above listed drugs and Thyro-Tabs pose no significant safety risk due to name confusion, and therefore, the proprietary name, Thyro-Tabs, is not objectionable.

2. DDMAC – no objections

¹ MICROMEDEX Healthcare Intranet Series, 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.), Emergindex, Reprdisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

² American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

⁴ Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 91 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Thyro-Tabs with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Thyro-Tabs (see below). These prescriptions were scanned into a computer and were then 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.

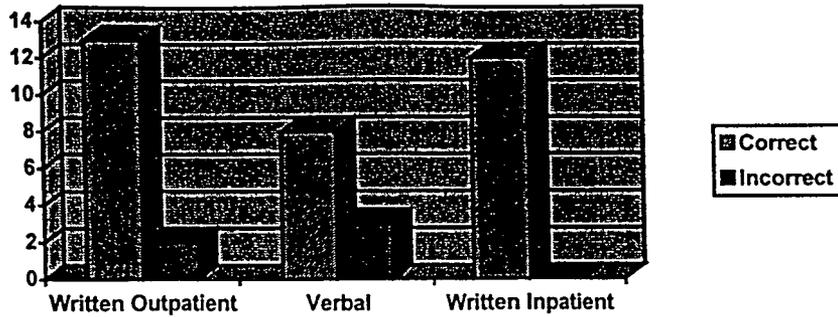
<u>HANDWRITTEN PRESCRIPTION</u>	<u>VERBAL PRESCRIPTION</u>
<u>Outpatient RX:</u> Thyrotabs 100 mcg #30 Sig: One tablet every day	Thyrotabs 100 mcg. #30 Sig: One tablet daily
<u>Inpatient RX:</u> Thyrotabs 100 mcg daily	

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Outpatient	30	15(50%)	13	2
Verbal	31	11(36%)	8	3
Written Inpatient	30	12(40%)	12	0
Total	91	38(42%)	33(87%)	5(13%)

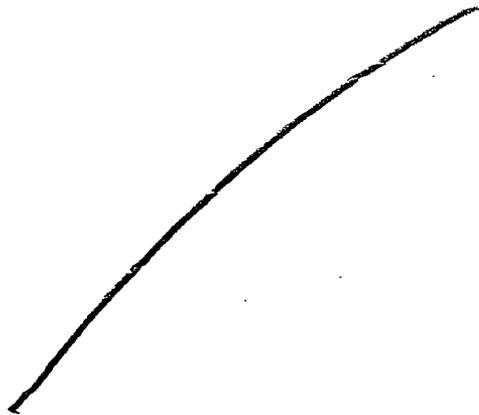


Eighty-seven percent of the participants responded with the correct name, Thyrotab (studies set up without “-”, since it is unlikely that practitioner will remember to write out the whole name with an hyphen. The incorrect written and verbal responses are as follows in Table II.

Table II

	<u>Incorrectly Interpreted</u>
Written Outpatient	Thyrotatan
	Myratab
Verbal	Zerotab
	Serotab

C. SAFETY EVALUATOR RISK ASSESSMENT



III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

We have no significant comments. However, we would recommend changing the statement “Caution: Federal law prohibits dispensing without prescription” to “Rx Only”

RECOMMENDATIONS:

1. OPDRA has no objections to the use of the proprietary name, Thyrotab (without hyphen).
2. OPDRA recommends the above labeling revisions 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.

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 further questions or need clarifications, please contact Peter Tam at 301-827-3241.

PT 6/6/06

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

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

CC:

NDA - 21-116

Office Files

HFD-510; DivFiles; Steve McCort, Project Manager, DMEDP

HFD-510; Solomon Sobel, M.D., Division Director, DMEDP

HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)

HFD-440; Lanh Green, Safety Evaluator, DDREII, OPDRA

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

NDA Filing Memorandum
Office of Clinical Pharmacology and Biopharmaceutics

NDA #:	21-116	Priority Type:	S
IND #:	57,315	Indication:	Hypothyroidism
Brand:	Thyro-Tabs®	Submission Date:	8/20/99
Generic:	Levothyroxine Sodium, USP	UFGD:	8/14/99 00 00
Sponsor:	Lloyd	Route of Administration:	Oral
Team Leader:	Hae-Young Ahn	Division:	HFD-870
Reviewer:	Steven B. Johnson	Medical Division:	DMEDP / HFD-510

<i>NDA Inclusion Items</i>	Yes	No	Not Applicable	Request for Information
Accurate Table of Contents?	X			
Human Studies Tabular Listing?	X			
HPK Summary?	X			
Study Synopses?	X			
Labeling?	X			
<i>Bioavailability and Bioequivalence Studies</i>				
ADME Study				
Relative BA	X			
BE (dosage form equivalence)	X			
Food-Drug Interaction			X	
IVIVc			X	
Reference Bioanalytical & Analytical Methods	X			
Dissolution Profiles	X			

This Application is filable at this time.

LSI

Steven B. Johnson, Pharm.D., FDA/CDER/OPS/OCPB/DPE-II

Date: 4 Oct. 99

LSI

Hae-Young Ahn, Ph.D., Team Leader; FDA/CDER/OPS/OCPB/DPE-II

Date: 10/5/99

CC: NDA 21-116, HFD-510 (MccortS), HFD-870 (ChenME, AhnH, FosslerM, JohnsonST), CDR (MurphyB)



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2002

To: Joseph Denhart,	From: Steve McCort
Company: Lloyd Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 712-246-5245	Fax number: 301-443-9282
Phone number: 800-831-004	Phone number: (301) 827-6415
Subject: Discipline Review Completed for NDA 21-125	

Total no. of pages including cover: 20

Comments:

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.

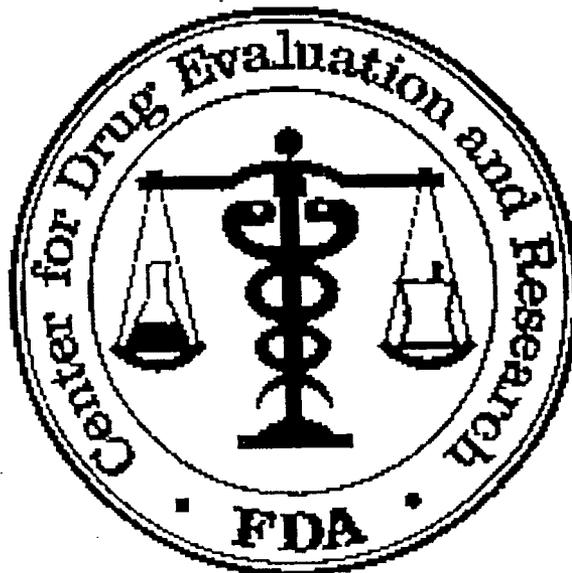
Document to be mailed: YES NO

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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: October 8, 1999



TO:

Name: **Dr. Denhart**

Fax No: 712-246-5245

Phone No: 712-246-4000

Location: **W.E. LLOYD Inc.**

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: **FDA, Division of
Metabolic and Endocrine
Drug Products**

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NDA 21-116

Pharm Requests for information



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: ¹⁰
~~8~~-24-02

To: STUART JOHNSON

From: Division of Metabolic and Endocrine Drug Products

Company: LLOYD INC

Fax number: 712-246-5245

Fax number: (301) 443-9282

Phone number: 712-246-4000

Phone number: 301-827-6415

Subject: re letter NDA 2116

Total no. of pages including cover:

Comments:

Document to be mailed: YES NO

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FAX of letter sent ¹⁰
~~8~~-24-02
 and received by Stuart Johnson
 of LLOYD INC at 4:00 pm.

 *** TX-REPORT ***

TRANSMISSION OK

TX/RX NO 0656
 CONNECTION TEL 917122465245
 CONNECTION ID
 ST. TIME 10/24 15:14
 USAGE T 08'34
 PGS. SENT 19
 RESULT OK



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: 8-24-02

To: STUART JOHNSON	From:
Company: LLOYD INC	Division of Metabolic and Endocrine Drug Products
Fax number: 712-246-5245	Fax number: (301) 443-9282
Phone number: 712-246-4000	Phone number: 301-827-6415
Subject: Rx letter NDA 2116	

Total no. of pages including cover:

Comments:

 Document to be mailed: YES NO

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INCORPORATED
(712) 246-4000

P.O. BOX 130 • 604 WEST THOMAS AVE. • SHENANDOAH, IOWA 51801-0130 U.S.A. • FAX (712) 246-5245

TELECOPIER TRANSMISSION

Date: 22 October 2002

To: Mr. Steve McCort
Project Leader
Center for Drug Evaluation and Research/FDA
Division of Metabolic and Endocrine Drug Products (HFD-150)
5600 Fishers Lane
Rockville, Maryland 20857
Fax #: (301) 443-9282

From: Stuart Johnson
Vice-President of Operations
Lloyd, Inc.
e-mail: sjohnson@lloydinc.com
FAX #: (712) 246-5245

Total Number of pages Transmitted (including cover sheet): Five (5)

Reference: Thyro-Tabs — labeling prototype layout

Dear Mr. McCort

Attached is a prototype of the labeling copy for the Thyro-Tabs — for one strength (75 µg) tablet and an example of the — on the —

The — design consists of a —

The first page is the copy for the outside of the —
copy for the inside front cover of the —

The second page is the

The third page is an example of the —
will contain —

Each

"Also attached is a revised copy of the last page of the package insert indicating the unber :
of tablets in the —

4 Draft Labeling Page(s) Withheld

LLOYD

INCORPORATED

(712) 246-4000

P.O. BOX 130 • 604 WEST THOMAS AVE. • SHENANDOAH, IOWA 51601-0130 U.S.A. • FAX (712) 246-5245

TELECOPIER TRANSMISSION

Date: 21 October 2002

To: Dr. David Lewis
Chemistry Reviewer
Center for Drug Evaluation and Research/FDA
Division of Metabolic and Endocrine Drug Products (HFD-150)
5600 Fishers Lane
Rockville, Maryland 20857
Fax #: (301) 443-9282

From: Stuart Johnson
Vice-President of Operations
Lloyd, Inc.
e-mail: sjohnson@lloydinc.com
FAX #: (712) 246-5245

Total Number of pages Transmitted (including cover sheet): Four (4)

Reference: Revised storage statement for Thyro-Tabs

Dear Dr. Lewis

Attached are copies of the last page of the package insert and representative samples of the immediate container labeling with the modified storage statement requested during your telephone call of 18 October 2002.

G. I. Doe 10/20/02

14 Draft Labeling Page(s) Withheld



P.O. BOX 130 • 604 WEST THOMAS AVE. • SHENANDOAH, IOWA 51901-0130 U.S.A. • FAX (712) 246-5245

TELECOPIER TRANSMITTAL

Date: 14 October 1999

To: Steve McCort
Project Leader
Food and Drug Administration
Division of Metabolic and
Endocrine Drug Products, HFD-510
Rockville, Maryland 20857
FAX: 301-443-9282

From: Joseph W. Denhart, DVM, MS
Vice-President Regulatory Affairs
and Quality Assurance
FAX: (712) 246-5245

Number of Pages (including cover sheet): Two (2)

Re: Response to your 08 October 1999 fax, NDA 21-116, Pharm
Requests for Information

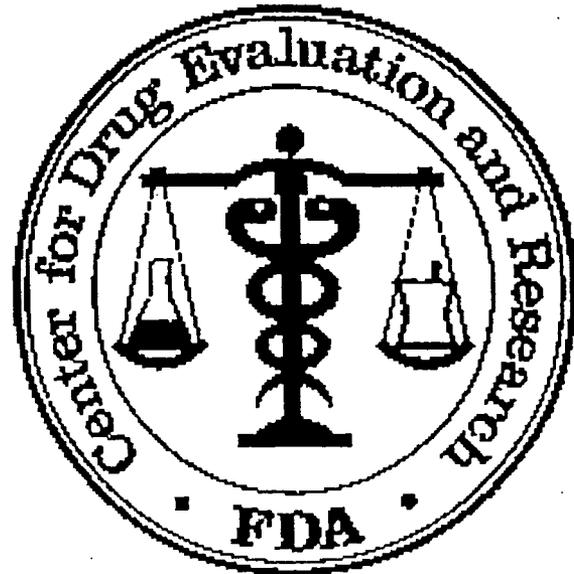
Message:

Appended is the letter that you asked that we fax to you for
delivery by you to Dr. Steigerwalt. Please call us at 712-246-
4000 or fax us at 712-246-5245 if you need additional
information.

Joe Denhart

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: October 8, 1999



TO:

Name: **Dr. Denhart**

Fax No: 712-246-5245

Phone No: 712-246-4000

Location: W.E. LLOYD Inc.

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: FDA, Division of
Metabolic and Endocrine
Drug Products

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NDA 21-116

Pharm Requests for information

**Recommendations for submission of preclinical data to support
Levothyroxine products for replacement therapy**

NDA's for replacement therapies with levothyroxine products require no specific preclinical studies if the product fulfills purity and biological activity specifications. In general, a brief summary of published preclinical data should suffice. The sponsor should supply pertinent reprints from published toxicology studies, particularly if reference is to be made in the label to specific animal data. For example, if there are any chronic toxicology or specific reproductive toxicology studies published that might identify the No Observed Adverse Effect Levels (NOAEL) and define the potential toxicities, these should be submitted. A submission of extensive collections of publications is not necessary.

The need for preclinical studies might be considered in cases of new formulations, particularly if they result in extensive changes in PK/PD parameters compared to previously marketed products. If the new formulation contains non-GRAS inactive ingredients, available published data which support the safety of the excipient may be acceptable in lieu of new preclinical studies with the new formulation if such data support the safe use of the product. The specific recommendations for preclinical studies under these circumstances will be determined on a case-by-case basis.

TELECOPIER TRANSMITTAL

Date: 12 January 1999
To: Steve McCort
Project Manager
FDA, Division of Metabolic and Endocrine Drug Products
FAX: 301-443-9282
From: Joseph W. Denhart, DVM, MS
Vice-President Regulatory Affairs
and Quality Assurance
FAX: (712) 246-5245

Number of Pages (including cover sheet): Two (2)

Re: Questions concerning IND 57,315: Levothyroxine Sodium Tablets
REQUEST FOR COMMUNICATION

Mr. McCort:

This is a written follow-up to our telephone discussion yesterday regarding the four issues I had addressed in a voice mail message to you 03 January 1999. Three of the questions were also presented during our conference with you and other FDA personnel on 14 December 1998 and an additional one has resulted from the medical comments made to our IND that you faxed to us 28 December 1998.

1. We indicated that our reference solution for the two-way crossover study would be levothyroxine sodium for injection, USP, 200 mg/vial from Knoll Pharmaceuticals. Our question was what is the number of vials that should be available at the clinical site as retention samples? We realize that 5 times the number of vials needed for release testing are required for retention samples. We are not aware of the number of vials required for release testing of this product but had proposed — vials. Dr. Foesler had indicated that he would check with OGD as to whether — vials were an adequate number. Since we are starting our studies the last of this month we need a response on this proposal as soon as possible.
2. The medical comments made to us pertaining to the submitted protocols - LLOY9801 and 9802 - stated that "1. Exclusion criteria should include: ... c. subjects taking any prescription or OTC medication within 1 month of study dosing." We will make every attempt to exclude individuals taking prescription or OTC medication within one month of starting each of the studies and would attempt to limit any medications after the study has commenced. However, we propose that should a subject take a medication during a washout period that each case be handled individually on a case-by-case basis to determine whether the medication would adversely affect the study and not that a subject would automatically be eliminated from the study.

0-12'

log message
Dr. Jean
+ message

Steve McCort, Project Manager
FDA, Division of Metabolic and Endocrine Drug Products
Page 2
12 January 1999

3. We would like a clarification of the acceptance for filing date vs. submission date question that we have discussed a couple of times with you to obtain clarification after our 14 December 1998 meeting. Hypothetically, if we made a NDA submission 15 September which was subsequently reviewed and was accepted for filing 15 November and another firm received approval of their NDA 16 September or some other date prior to the 15 November date would our submission be reviewed for approval as an NDA?
4. Dr. Wu had indicated during the 14 December 1998 conference that he would review the post-approval stability matrix design we had proposed and respond at a later date.

In addition, he gave some indication at the conference that perhaps our proposal for stability testing that we proposed to file with our NDA might have been excessive. Dr. Wu indicated 3 low, 3 high strengths and 2 or 3 in the middle would probably be adequate. We had proposed that 3 low strengths, and one of each of the other strengths would have at least \rightarrow stability data at filing the NDA and that the middle and high strengths would each have two more stability tests started on post-approval batches.

We would like Dr. Wu's comments on our stability proposals for NDA filing as soon as possible as we are manufacturing batches now and need the minimum stability information that would be expected for filing the NDA.

We would like a telephone response to these questions this week, if possible. Thank you for your help.

Joe Denhart

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: August 13, 1999



TO:

Name: **Dr. Denhart**

Fax No: 712-246-5245

Phone No: 712-246-4000

Location: **W.E. LLOYD Inc.**

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: **FDA, Division of
Metabolic and Endocrine
Drug Products**

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Comments: Stability CMC Study guidelines for NDA submission for L-Thyroxine

GUIDELINES FOR SUBMISSION OF CMC STABILITY STUDIES FOR NDA FOR L-THYROXINE

1. Stability studies must be conducted using ICH-recommended storage conditions, $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\%$ RH long term studies; $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\%$ RH for accelerated studies and $40^{\circ}\text{C}/60\%$ RH intermediate studies.
2. The formulation for the drug product may not contain an overage for the purpose of counteracting potency loss during stability. The product must be targeted for 100% upon release of product.
3. A bracketing plan that includes stability data for three lots of the lowest strength, three lots of the highest strength, and two lots of an intermediate strength is acceptable for the drug product.
4. The minimum acceptable size for stability testing is 10% of a full commercial (marketing) batch.
5. The minimal amount of stability data needed at the time of submission of the NDA for filing is 6 months of real time data and 3 months accelerated time data from ongoing studies for the drug product. Additional stability data may be submitted to the NDA during the review process when the data is collected to support the application.
6. The Sponsor should follow the recommendations outlined in the ICH guidance on submitting stability data.

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: July 16, 1999



TO:

Name: **Dr. Denhart**

Fax No: 712-246-5245

Phone No: 712-246-4000

Location: **W.E. LLOYD Inc.**

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: **FDA, Division of
Metabolic and Endocrine
Drug Products**

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Comments:

Comments for L-thyroxine when NDA submitted (clinical)

EC: IND 59,315
HFD-510 / DIV FILE
HFD-510 / SMCCOMY

The following comment pertains to additional information needed when the NDA for L-Thyroxine is submitted:

Summarize, by individual bioavailability study, the results of each safety parameter monitored, noting any abnormalities that occurred and if they were clinically significant.

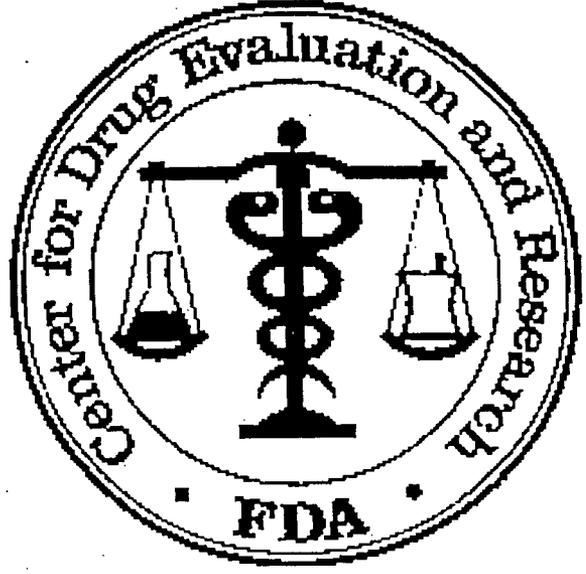
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McCORT

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: May 21, 1999



TO:

FROM:

Name: Dr. Denhart

Name: Steve McCort

Fax No: 712-246-5245

Fax No: 301-443-9282

Phone No: 712-246-4000

Phone No: 301-827-6415

Location: W.E. LLOYD Inc.

Location: FDA, Division of
Metabolic and Endocrine
Drug Products

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Comments:

Comments for L-thyroxine when NDA submitted (Pediatric Rule)

cc:

IND 57,315

FD-510 / DIV FILE

FD-510 / Smcort / J Tame

(2)

REQUEST FOR L-THYROXINE (when NDA submitted):

IND 57,315

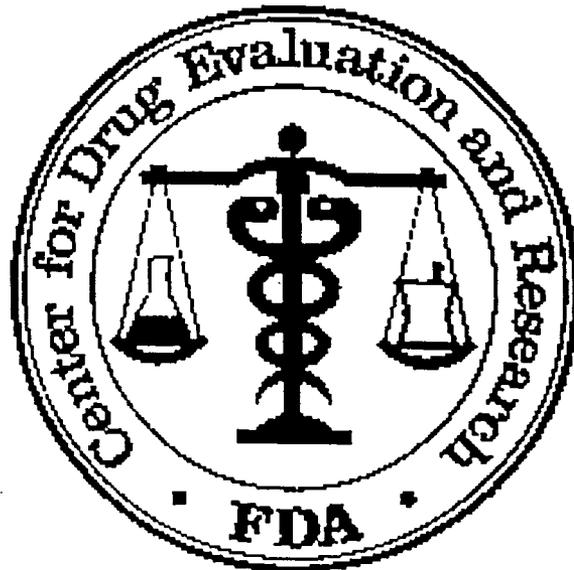
Due to the Pediatric Rule, we are asking that you submit several representative articles from the published literature to support your product in pediatric age patients; efficacy-including dosing guidelines- and safety.

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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: FEBRUARY 17, 1999



TO:

Name: **Dr. Denhart**

Fax No: 712-246-5245

Phone No: 712-246-4000

Location: **W.E. LLOYD Inc.**

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: **FDA, Division of
Metabolic and Endocrine
Drug Products**

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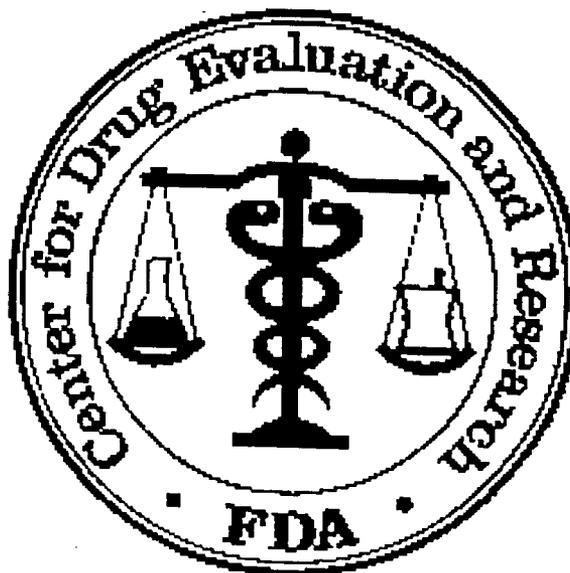
Comments:

Answer to question #3 of Lloyd's January 12, 1999 letter to FDA.

1 Page(s) Withheld

FOOD AND DRUG ADMINISTRATION -
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: January 25, 1999



TO:

Name: **Dr. Deinhart**

Fax No: 712-246-5245

Phone No: 712-246-4000

Location: **W.E. LLOYD Inc.**

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: **FDA, Division of
Metabolic and Endocrine
Drug Products**

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Comments:

Fax of article to answer question #2 of January 12, 1999 from Firm regarding IND 57, 315; L-Thyroxine

REVIEW ARTICLE

DRUG THERAPY

ALASTAIR J. J. WOOD, M.D., *Editor*

DRUGS AND THYROID FUNCTION

MARTIN I. SURKS, M.D., AND RUBENS SIEVERT, M.D.

TESTING of thyroid function is common in clinical practice. Many patients who are tested, including those who have or are receiving treatment for thyroid disease, take medications that may affect thyroid function. Therefore, the possible effect of these drugs both on the results of thyroid-function tests and on the effectiveness of treatment must always be considered in decisions regarding patient care.

The pathways of thyroid hormone synthesis, secretion, transport in the circulation, and metabolism offer numerous targets for drug interaction (Fig. 1 and 2). Normal thyroid secretion depends on thyrotropin (TSH). Secretion of TSH is, in turn, inhibited by thyroid hormones and stimulated by thyrotropin-releasing hormone (TRH). Iodide in serum is trapped by thyroid cells, after which it is oxidized and incorporated into some of the tyrosine residues of thyroglobulin, which then couple to form thyroxine (T_4) and triiodothyronine (T_3).

The thyroid gland normally contains large stores of thyroglobulin, most of which is in the lumen of the thyroid follicles. When thyroglobulin is resorbed into the follicular cells of the thyroid and hydrolyzed, T_4 and T_3 are secreted into the circulation. There they are bound to specific serum-binding proteins, so that very little circulates as free T_4 or T_3 . In extrathyroidal tissues, T_4 is converted to T_3 by the action of several T_4 5'-deiodinases; this process generates about 80 percent of the circulating T_3 . About 80 percent of T_4 and T_3 is metabolized by deiodination and 20 percent by non-deiodinative pathways that include conjugation with glucuronides and sulfates, decarboxylation, and deamination.¹ In tissues, T_3 and — to a much smaller extent — T_4 are bound to specific nuclear receptor proteins that interact with regulatory regions of genes, influencing their expression.

In this paper we shall discuss the effects of groups of drugs on the production, secretion, transport, and metabolism of T_4 and T_3 and on the absorption of exogenously administered T_4 .

TSH DRUGS AFFECTING THE SECRETION OF TSH

Measurement of serum TSH is the single best test of thyroid function, because of the sensitivity of TSH secre-

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tion to very small changes in serum T_4 and T_3 concentrations. Serum TSH concentrations are low in patients with hyperthyroidism and high in those with primary hypothyroidism. When hypothyroidism results from hypothalamic or pituitary disease, serum TSH values are usually low or normal, but occasionally they are high because of the secretion of biologically inactive TSH.^{2,3}

Several drugs decrease TSH secretion and lower serum TSH concentrations, although not to values as low as those found in patients with hyperthyroidism (Table 1). These agents are dopamine (in doses of at least 1 μ g per kilogram of body weight per minute),^{4,8} glucocorticoids (e.g., dexamethasone, in doses of 0.5 mg or more per day or hydrocortisone in doses of 100 mg or more per day),^{9,10} and octreotide (in doses of more than 100 μ g per day), which is a somatostatin analogue used for the treatment of acromegaly and certain other hormone-excess syndromes.^{11,12} Patients who are receiving long-term glucocorticoid or octreotide therapy do not, however, have sustained reductions in TSH secretion, nor does hypothyroidism develop, probably because of the effect of decreased thyroid hormone secretion in increasing TSH secretion. Patients who require infusions of dopamine for more than a few days may have reductions in secretion by the thyroid, which are difficult to distinguish from the changes in serum T_4 and T_3 concentrations that result from the underlying illness.

DRUGS AFFECTING THE SECRETION OF THYROID

HORMONE $\checkmark T_4$ $\checkmark T_3$ $\checkmark TSH$

In addition to methimazole and propylthiouracil, which are given deliberately to decrease thyroid hormone production in patients with hyperthyroidism, several other commonly used drugs may decrease thyroid hormone secretion. These include lithium carbonate and iodine-containing medications (Table 1).

Drugs That Cause Hypothyroidism $\checkmark T_4$ $\checkmark T_3$ $\checkmark TSH$

Lithium interferes with thyroid hormone synthesis and decreases thyroid hormone secretion. Long-term lithium treatment results in goiter in up to 50 percent of patients, subclinical hypothyroidism in up to 20 percent, and overt hypothyroidism in up to 20 percent.¹³⁻¹⁵ Many lithium-treated patients have antithyroid antibodies in their serum; among them about 50 percent have subclinical hypothyroidism, as compared with 15 percent of patients with no antithyroid antibodies.¹⁵ The antithyroid antibodies probably indicate the presence of preexisting chronic autoimmune thyroiditis, which would be expected to increase sensitivity to the antithyroid actions of lithium, but which could, alternatively, be induced by lithium.

Normal subjects given 1 to 2 mg of inorganic iodide per day (in addition to their usual diet) have a transient decrease in T_4 and T_3 secretion and a transient increase in TSH secretion.¹⁶ The decrease in T_4 and T_3 secretion is much greater, but is usually also transient, in patients with hyperthyroidism.¹⁷ However, in patients with chron-

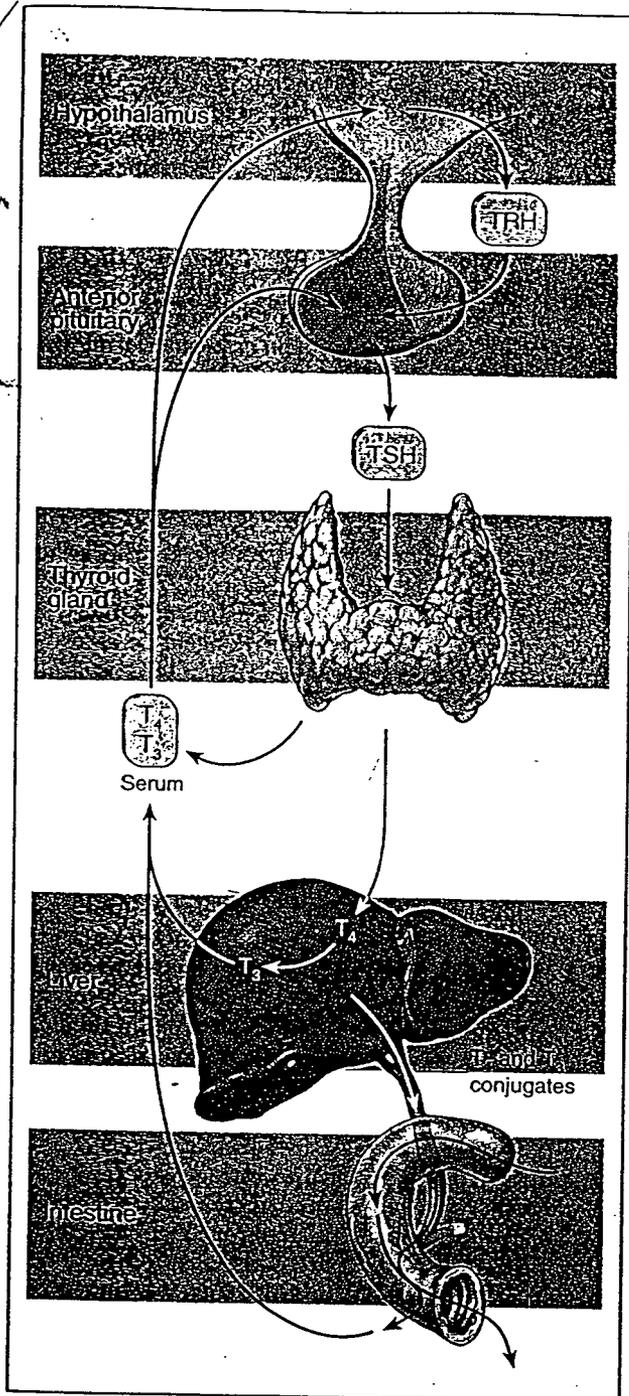


Figure 1. The Hypothalamic-Pituitary-Thyroid Axis and Extra-thyroidal Pathways of Thyroid Hormone Metabolism.

Triiodothyronine (T_3) and thyroxine (T_4) inhibit the secretion of thyrotropin (TSH) both directly and indirectly, by inhibiting the secretion of thyrotropin-releasing hormone (TRH). TSH stimulates the synthesis and secretion of T_4 and T_3 by the thyroid gland. T_4 is converted to T_3 in the liver (and many other tissues) by the action of T_4 monodeiodinases. Some of the T_4 and T_3 is conjugated with glucuronide and sulfate in the liver, excreted in the bile, and partially hydrolyzed in the intestine; the T_4 and T_3 formed there may be reabsorbed. Drug interactions can occur at any of these sites.

risks posed by the use of radiographic contrast agents for coronary angiography or computed tomography is of particular concern because of the widespread use of these procedures. The contrast agents usually are given in doses of 100 to 150 ml for diagnostic testing and up to 400 to 500 ml when coronary angioplasty is also performed. Even though the parent compounds are excreted in 10 to 14 days, minimal deiodination (e.g., only 0.1 percent) will result in the release of as much as 14 to 175 mg of iodide. Oral cholecystographic agents and amiodarone, especially, are much more slowly excreted and may cause more prolonged hypothyroidism.

Several other drugs have been reported to cause hypothyroidism. Long-term treatment with aminoglutethimide results in small decreases in serum T_4 and T_3 concentrations and increases in serum TSH concentrations, although all the values remain within the normal range in most patients.^{18,19} Many other drugs, such as tolbutamide and the sulfonamides, have been reported to cause hypothyroidism in occasional patients, but a direct cause-and-effect relation has rarely been proved.²⁰

Drugs That Cause Hyperthyroidism T_4 T_3 TSH

Iodide and drugs that contain pharmacologic amounts of iodide (Table 2) may also cause hyperthyroidism in euthyroid patients with thyroid autonomy — that is, multinodular goiter or hyperfunctioning thyroid adenoma — and in patients with these disorders and also Graves' disease who live in areas of severe iodine deficiency.^{16,21,22} The hyperthyroidism may develop within three to eight weeks after iodine or drug administration and may persist for several months after therapy is discontinued. Amiodarone may also induce hyperthyroidism by causing thyroiditis.²³

DRUGS AFFECTING T_4 ABSORPTION T_4 T_3

The gastrointestinal tract has a role in thyroid physiology because T_4 and T_3 conjugates are excreted in the bile and partially deconjugated in the intestine, releasing small amounts of T_4 and T_3 for reabsorption. A very small portion of the daily production of T_4 and T_3 , less than 10 percent, is excreted in the stool.²⁴ In people with normal thyroid function, this pathway of T_4 and T_3 recirculation contributes so little to hormone availability that patients who have gastrointestinal disease or are receiving drugs that decrease T_4 absorption do not have abnormal thyroid function.

In patients receiving oral T_4 , however, the situation is

ic autoimmune thyroiditis, in patients with hyperthyroidism who have received radioactive iodine therapy or have undergone partial thyroidectomy, and probably in patients whose thyroid gland is damaged in any other way, iodide may induce persistent hypothyroidism.¹⁶ In these patients, unlike normal subjects and previously untreated patients with hyperthyroidism, adaptation to the antithyroid action of iodide does not occur.

In addition to inorganic iodide, there are many iodine-containing organic compounds used in clinical practice that are partially deiodinated in vivo and therefore can affect thyroid function (Table 2). The

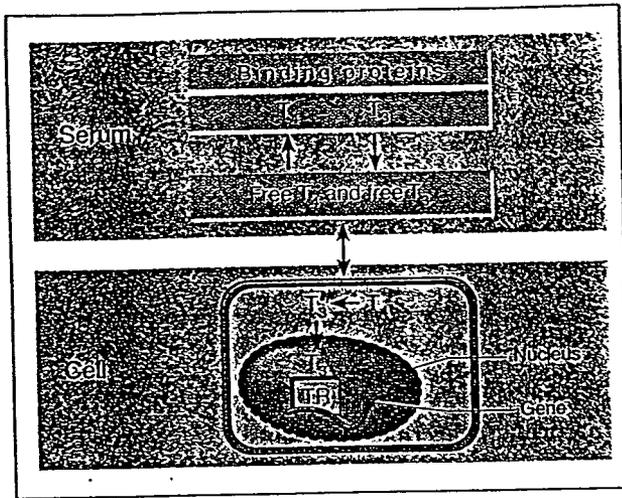


Figure 2. Thyroid Hormone Transport in Serum and Hormone Action.

The binding proteins include thyroxine-binding globulin, transthyretin, and albumin. Drugs may alter the production or clearance of a binding protein or inhibit the binding of thyroxine (T₄) and triiodothyronine (T₃) to the protein. TR denotes thyroid receptor.

different. Normally, about 80 percent of a usual dose (50 to 150 µg per day) is absorbed, mostly in the jejunum and the upper part of the ileum. In patients who are dependent on exogenous T₄, drugs that decrease T₄ absorption may induce hypothyroidism (Table 1). Among untreated patients, the severity of hypothyroidism might be expected to increase.

The bile acid sequestrants colestipol and cholestyramine bind T₄ and decrease its absorption, and they have proved useful in the treatment of patients with exogenous hyperthyroidism.²⁵ A decrease in serum T₄ concentrations and an increase in serum TSH concentrations occurred when cholestyramine was administered to T₄-treated patients with hypothyroidism.²⁶ In normal subjects, thyroid function is not affected by these drugs.²⁷

Decreased absorption of T₄ and increases in serum TSH concentrations have also been reported in T₄-treated patients with hypothyroidism who are given aluminum hydroxide,^{28,29} ferrous sulfate,³⁰ or sucralfate,³¹ but absorption of T₄ was not decreased in the majority of the patients treated with ferrous sulfate and sucralfate who were studied.^{30,32,33} The interactions can be minimized by having the patient take T₄ and the other drug several hours apart. Therefore, even though interference with T₄ absorption seems to occur in relatively few patients, it is prudent to advise all patients to take their T₄ and other medications at different times.

DRUGS AFFECTING T₄ AND T₃ TRANSPORT IN SERUM

More than 99 percent of the T₄ and T₃ in serum is bound to one of the three major transport proteins: thyroxine-binding globulin (TBG), transthyretin, and al-

bumin.^{34,35} TBG binds approximately 70 percent of serum T₄ and a larger fraction of serum T₃; it is therefore the most important of the binding proteins. Although less than 0.1 percent of T₄ and T₃ circulates unbound to proteins, it is the concentration of free hormone that determines the action of the hormones in tissues. Alterations in the serum concentrations of these binding proteins alter serum total T₄ and T₃ concentrations, but not serum concentrations of free T₄ and T₃; therefore the patient remains euthyroid. Drugs may affect T₄ and T₃ transport either by raising or lowering the serum concentration of a binding protein or by interfering with the binding of T₄ and T₃ to a binding protein. Nearly all the drugs that alter T₄ and T₃ transport do so by altering the serum concentration of TBG or its affinity for T₄ and T₃.

Increases in Serum TBG Concentrations

The most common causes of an increase in serum TBG concentrations are an increase in estrogen production and the administration of estrogen, either as a component of an oral contraceptive agent or as estrogen-replacement therapy (Table 1).³⁶⁻⁴⁰ TBG is a glycoprotein that is synthesized in the liver. Estrogens produce increased sialylation of TBG, which decreases its rate of clearance and raises its serum concentration.³⁵ The increase in TBG in serum is dose-dependent. The usual doses of ethinyl estradiol (20 to 35 µg per day) and conjugated estrogen (0.625 mg per day) raise serum TBG concentrations by approximately 30 to 50 percent and serum T₄ concentrations by 20 to 35 percent.³⁶⁻⁴⁰ The increases begin within two weeks, and a new steady state is attained in four to eight weeks. In women with hypothyroidism who are receiving T₄ and become pregnant, an increase of 45 percent in the dose is needed, on average, to maintain normal serum TSH concentrations.⁴¹ Thus, the increase in serum total T₄ concentrations induced by estrogen occurs as a result of at least a transient increase in T₄ secretion.

Addition of a progestogen to estrogen therapy does not alter the estrogen-induced increase in the serum TBG concentrations, and progesterone alone has no effect. Oral estrogen has a first-pass effect on the liver; transdermal administration of estrogen does not raise serum TBG or T₄ concentrations, even though serum estrogen concentrations are comparable to those measured after oral administration.³⁷ Tamoxifen has weak estrogen-agonist effects in the liver and raises serum TBG concentrations slightly.⁴²

Serum TBG concentrations are increased in about 50 percent of patients who use heroin for long periods or are treated with methadone.⁴³⁻⁴⁵ Many of these patients also have abnormal liver function, so that the increase in serum TBG may result from liver disease rather than from specific effects of these drugs.^{43,44} Cocaine use has not been associated with changes in serum TBG, T₄, or T₃ concentrations.⁴⁶

Mitotane and fluorouracil are also associated with increases in serum concentrations of total T₄ and T₃, but serum free T₄ and TSH concentrations remain nor-

Handwritten notes: TBG, T₃ Ru, T₄, T₃, free T₄.

Table 1. Drugs That Influence Thyroid Function.*

Drugs that decrease TSH secretion	
Dopamine	
Glucocorticoids	
Octreotide	
Drugs that alter thyroid hormone secretion	
Decreased thyroid hormone secretion	
Lithium	
Iodide	
Amiodarone	
Aminoglutethimide	
Increased thyroid hormone secretion	
Iodide	
Amiodarone	
Drugs that decrease T₄ absorption	
Colestipol	
Cholestyramine	
Aluminum hydroxide	
Ferrous sulfate	
Sucralfate	
Drugs that alter T₄ and T₃ transport in serum	
Increased serum TBG concentration	
Estrogens	
Tamoxifen	
Heroin	
Methadone	
Mitotane	
Fluorouracil	
Decreased serum TBG concentration	
Androgens	
Anabolic steroids (e.g., danazol)	
Slow-release nicotinic acid	
Glucocorticoids	
Displacement from protein-binding sites	
Furosemide	
Fenclofenac	
Mefenamic acid	
Salicylates	
Drugs that alter T₄ and T₃ metabolism	
Increased hepatic metabolism	
Phenobarbital	
Rifampin	
Phenytoin <i>dilantin</i>	
Carbamazepine <i>Tegretol</i>	
Decreased T ₄ 5'-deiodinase activity	
Propylthiouracil	
Amiodarone	
Beta-adrenergic-antagonist drugs	
Glucocorticoids	
Cytokines	
Interferon alfa	
Interleukin-2	

*TSH denotes thyrotropin, T₄ thyroxine, T₃ triiodothyronine, and TBG thyroxine-binding globulin.

mal.^{47,48} It is likely that these drugs also increase the serum concentration of TBG.

Decreases in Serum TBG Concentrations

In contrast to those treated with estrogens, patients taking androgens or anabolic steroids have decreased serum TBG and T₄ concentrations (Table 1).⁴⁹⁻⁵¹ These patients are clinically euthyroid, their serum free T₄ and TSH concentrations remain within the normal range, and their production and turnover of T₄ are normal. The administration of androgen to women with breast cancer who also had hypothyroidism and were being treated with T₄ induced hyperthyroidism, with an increase in serum free T₄ and a decrease in serum TSH concentrations.⁵² These results suggest that androgens

not only lower serum TBG concentrations but also slightly decrease T₄ production. A decrease in the serum TBG concentration also occurs during long-term glucocorticoid treatment.

Patients treated with nicotinic acid may have decreased serum TBG and T₄ concentrations.⁵³⁻⁵⁵ In one study, treatment of hypercholesterolemia with colestipol and niacin (3 to 6 g per day) resulted in a 25 percent decrease in the serum TBG concentration and a small decrease in the serum T₄ concentration (1.5 μg per deciliter [1.9 nmol per liter])⁵³ but no change in the serum free T₄ and TSH concentrations. The changes were probably caused by the niacin, since colestipol alone has no effect on thyroid function.²⁷

Inhibition of the Binding of T₄ and T₃ to TBG

At therapeutic concentrations, several drugs inhibit the binding of T₄ and T₃ to TBG to varying degrees (Table 1). The initial effect of these drugs is to increase serum free T₄ concentrations, because the drug displaces T₄ from TBG; continued administration, however, results in a decrease in serum T₄, normal serum free T₄, and normal serum TSH concentrations.

Furosemide has no effect at the usual therapeutic concentrations, but large intravenous doses (more than 80 mg) result in a transient increase in serum free T₄ concentrations and a decrease in serum total T₄ concentrations.⁵⁶⁻⁵⁸ The changes in serum total and free T₄ vary depending on the length of time between the administration of the drug and the collection of the sam-

Table 2. Iodine Content of Some Iodine-Containing Medications and Radiographic Contrast Agents.

SUBSTANCE	AMOUNT OF IODINE
Expectorants	
Iophen	25 mg/ml
Organidin (iodinated glycerol)	15 mg/tablet
Par Glycerol	5 mg/ml
R-Gen	6 mg/ml
Iodides	
Potassium iodide (saturated solution)	~25 mg/drop
Pima syrup (potassium iodide)	255 mg/ml
Lugol's solution (potassium iodide + iodine)	~7 mg/drop
Iodo-Niacin	115 mg/tablet
Antiasthmatic drugs	
Mudrane	195 mg/tablet
Elixophyllin-KI (theophylline) elixir	6.6 mg/ml
Iophylline	2 mg/ml
Antiarrhythmic drugs	
Amiodarone	75 mg/tablet
Antiamoebic drugs	
Iodoquinol	134 mg/tablet
Topical antiseptic agents	
Povidone-iodine	10 mg/ml
Clioquinol cream	12 mg/g
Douches	
Povidone-iodine	10 mg/ml
Radiographic contrast agents	
Iopanoic acid	333 mg/tablet
Iodate sodium	308 mg/tablet
Intravenous preparations	140-380 mg/ml

ple, on the rate of renal clearance of the drug, and on the serum concentrations of albumin (which also binds furosemide) and TBG. Several nonsteroidal antiinflammatory drugs have similar effects.⁵⁷

Salicylates (in doses of >2.0 g per day) and salicylate (in doses of 1.5 to 3.0 g per day) also inhibit the binding of T₄ and T₃ to TBG; salicylates inhibit binding to transthyretin as well.⁵⁹ As with furosemide, the initial effect is an increase in serum free T₄ concentrations.⁶⁰ When therapeutic serum concentrations are sustained, salicylates result in a 20 to 30 percent decrease in serum total T₄ concentrations and normal serum free T₄ concentrations. Salsalate may result in a greater decrease in the serum T₄ concentration (by 30 to 40 percent) and a decrease in the serum free T₄ index,⁶¹⁻⁶³ but the latter change is probably an in vitro artifact.⁶⁰

Serum free T₄ concentrations increase transiently after the administration of heparin.⁶⁴ This increase is caused in vitro by the inhibition of protein binding of T₄ by the free fatty acids generated as a result of the ability of heparin to activate lipoprotein lipase.⁶⁵⁻⁶⁷

METABOLISM OF T₄ AND T₃

T₄ and T₃ are metabolized mostly by deiodination but also by glucuronidation and sulfation.^{1,68} The activity of the enzymes that facilitate these reactions is affected by a variety of drugs (Table 1). Their actions, in general, vary according to whether the patient has normal pituitary-thyroid function and therefore can compensate for any alteration in T₄ and T₃ metabolism or has hypothyroidism and therefore little ability to increase whatever thyroid secretion persists. Among these drugs are phenobarbital and rifampin,⁶⁸⁻⁷¹ which increase T₄ and T₃ metabolism by stimulating hepatic microsomal drug-metabolizing enzyme activity. Hypothyroid patients treated with T₄ may become hypothyroid again when rifampin is administered.⁷¹

Phenytoin and carbamazepine have more complex effects. Like phenobarbital and rifampin, the two anticonvulsant drugs increase the rate of T₄ and T₃ metabolism and can cause hypothyroidism in patients with hypothyroidism who are treated with T₄.⁷² Phenytoin and carbamazepine also cause a decrease of 20 to 40 percent in serum total and free T₄ concentrations and a smaller decrease in serum total and free T₃ concentrations in patients who have no thyroid disease.⁷³⁻⁷⁶ Most have normal serum TSH concentrations, are clinically euthyroid, and have a normal resting metabolic rate.^{73,77} These paradoxical findings, notably the decrease in serum free T₄ and T₃ concentrations in the absence of any other evidence of hypothyroidism, may be explained by recent measurements of free T₄ in undiluted human serum by ultrafiltration (Surks MI, Defesi CR: unpublished data). In these assays, in contrast to previous measurements in which serum was diluted, serum free T₄ concentrations were normal in patients treated with phenytoin and carbamazepine. Transient

hypothyroidism has been reported in a few patients with hypersensitivity reactions to phenytoin.²⁰

T₄ 5'-Deiodinase

Most of the T₃ produced outside the thyroid results from the action of the T₄ 5'-deiodinase (type I) that is found mainly in liver, kidney, and muscle.^{1,68} Drugs that inhibit this enzyme result in a decrease in T₃ production and lower serum T₃ concentrations (Table 1). Occasionally, serum T₄ concentrations increase as well.

Although amiodarone may cause either hypothyroidism or hyperthyroidism, most patients treated with amiodarone remain euthyroid but have altered serum T₄ and T₃ concentrations.^{21,78} Their serum total and free T₄ concentrations increase to the high-normal range or just above normal, and their serum T₃ concentrations decrease to low-normal. Serum TSH concentrations remain normal, although occasionally they are slightly high during the first several months of treatment.

Small decreases in serum T₃ concentrations occur in patients treated with large doses (>160 mg per day) of propranolol, and a few have small increases in serum T₄ concentrations.^{79,80} The patients are clinically euthyroid and have normal serum TSH concentrations. Among patients with hyperthyroidism, atenolol, alprenolol, and metoprolol decrease serum T₃ concentrations slightly, but serum T₄ concentrations do not change.^{81,82}

Large doses of glucocorticoids — for example, 4 mg of dexamethasone per day — also cause a 30 percent decrease in serum T₃ concentrations within several days.⁸³⁻⁸⁷ There is minimal short-term change in serum T₄ concentrations, but, as noted above, they may decline slightly during long-term glucocorticoid therapy because of decreased production of TBG.

THYROID DYSFUNCTION CAUSED BY CYTOKINES

Thyroid dysfunction may develop in patients with chronic inflammatory disorders or tumors who receive long-term treatment with cytokines. Therapy with interferon alfa is associated with the development of antithyroid microsomal (antithyroperoxidase) antibodies in 20 percent of patients, and some have transient hyperthyroidism, hypothyroidism, or both.⁸⁸⁻⁹⁰ Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Thyroid dysfunction has not been reported during treatment with interferon beta or gamma.^{91,92} Therapy with interleukin-2 was associated with transient painless thyroiditis in about 20 percent of patients.^{93,94}

CONCLUSIONS

Drugs can affect thyroid economy in numerous ways. They may cause hyperthyroidism or hypothyroidism, subclinical or overt hypothyroidism in patients treated with T₄, or abnormalities on any of the tests used to evaluate patients in whom thyroid dysfunction is suspected. Knowledge of the site of drug interaction and the physiologic features of the thyroid hormone system should enable the clinician to anticipate these changes.

-pp 1693-4 are references

MCCORT

DATE: December 28, 1998

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857



TO:

FROM:

Name: Dr. Deinhart

Name: Steve McCort

Fax No: 712-246-5245

Fax No: 301-443-9282

Phone No: 712-246-4000

Phone No: 301-827-6415

Location: W.E. LLOYD Inc.

Location: FDA, Division of
Metabolic and Endocrine
Drug Products

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above the above address by mail. Thank you.

Comments:

Comments for IND 57,315 L-Thyroxine Sodium

IND 57,315

HFD-510/10,4 R, LQ

HFD-510/SMCORT / J Tamick

MESSAGE CONFIRMATION

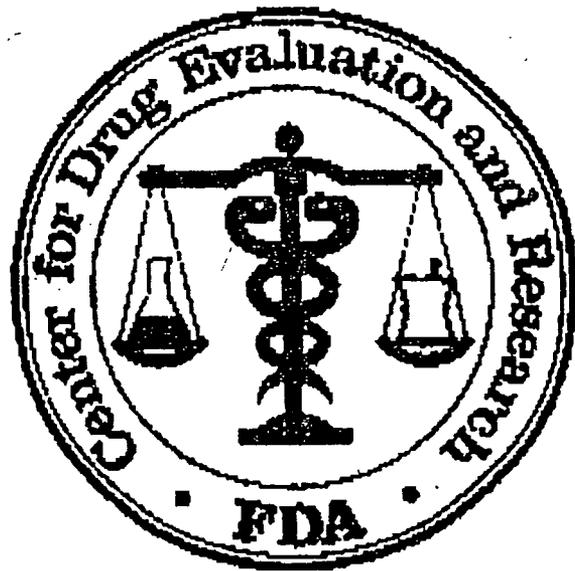
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ID=DMEDP-CDER-FDA

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51	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: December 28, 1998



TO:

Name: **Dr. Deinhart**

Fax No: 712-246-5245

Phone No: 712-246-4000

Location: **W.E. LLOYD Inc.**

FROM:

Name: **Steve McCort**

Fax No: 301-443-9282

Phone No: 301-827-6415

Location: **FDA, Division of
Metabolic and Endocrine
Drug Products**

med. CAL comments:

The following comments pertain to both submitted protocols- LLOY 9801 and 9802- and these comments should be conveyed to the sponsor:

1. Exclusion criteria should include:
 - a. lactating women
 - b. subjects taking medications known to affect thyroid hormone metabolism, e.g. oral contraceptives, androgens, anabolic steroids, etc.
 - c. subjects taking any prescription or OTC medication within 1 month of study dosing
 - d. subjects with a concurrent medical condition known to interfere with the absorption or metabolism of thyroid hormones.
2. A sufficiently sensitive TSH assay should be used to identify subtle abnormalities of thyroid function. Such subjects should be excluded from these studies.
3. In women of child-bearing potential, repeat the serum pregnancy test 24 hours before each drug treatment period in each protocol. The pregnancy test must be negative before another drug dose is administered.
4. Blood pressure and pulse should be monitored at baseline and periodically during the first 24 hours post levothyroxine sodium administration, and, again, at the 48 hour post-dose timepoint. It is recommended that an ECG be obtained at screening and only subjects with a normal ECG be enrolled. Consideration should be given to repeating the ECG at the end of the study, but it is optional.

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

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

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

LLOYD, Inc.
P.O. Box 130
604 West Thomas Ave.
Shenandoah, Iowa 51601-0130

2. PRODUCT NAME

Thyro-Tabs®
Levothyroxine Sodium; O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiido-L-tyrosine monosodium salt; L-3,3',5,5'-tetraiodothyronine sodium salt

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:

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

3. TELEPHONE NUMBER (Include Area Code)
(712) 246-4000

5. USER FEE LD. NUMBER

6. LICENSE NUMBER / NDA NUMBER
NDA 21-116

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)
- 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 COMMERCIALY (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 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.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
 W. E. Lloyd, D.V.M., Ph.D.	Chief Executive Officer	11 Aug 1999

FORM FDA 3397 (5/98)

APPLICANT NAME LLOYD

PRODUCT NAME THYRO TABS (LEVOTHYROXINE SODIUM TABLETS)

FORM MUST BE COMPLETED ASAP

1. YES User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMPS DATA ELEMENTS

SBA / small business
WAIVER
granted 8/19/99

2. YES NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well controlled trials. Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION	FEE	NO FEE
N _____	_____	FEE	NO FEE

4. YES NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, & review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N _____	_____	N _____	_____

5. P S PRIORITY OR STANDARD?

151

151

8/23/99

6. CSO SIGNATURE/DATE

SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

Galliers, Enid M

From: CDER DocAdmin, DFS
Sent: Friday, January 31, 2003 2:49 PM
To: Lewis, David B; McCort, Stephen M; Galliers, Enid M; Johnson, Steven B
Subject: DFS Email - N 021116 N 000 BB 04-Oct-2002 - Meeting Minutes



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Document room update the following:

	<u>Decision Date</u>	<u>Decision Code</u>
N 021116 N 000 BB 04-Oct-2002	31-Jan-2003	NR:NO REPLY NECESSARY

Document Type: Meeting Minutes

Submission Description: T-con minutes 10.09.2002 - CMC & BPH
pre-approval Thyro-Tabs

Author(s)/Discipline(s)

1. Enid Galliers, CSO

Signer(s)

1. Enid Galliers
24-Jan-2003
2. David Lewis
I see No problems with the minutes, as written.
31-Jan-2003

Supervisory Signer(s)

1. David Lewis
I see No problems with the minutes, as written.
31-Jan-2003

1 Page(s) Withheld

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0338 Expiration Date: March 31, 2003 See OMB Statement on page 2.	
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		FOR FDA USE ONLY	
		APPLICATION NUMBER	
APPLICANT INFORMATION			
NAME OF APPLICANT J. LOYD, Inc., of Iowa		DATE OF SUBMISSION 23 July 2001	
TELEPHONE NO. (Include Area Code) (712) 246-4000		FACSIMILE (FAX) Number (Include Area Code) (712) 246-5245	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 604 West Tomas Avenue Shenandoah, Iowa, USA 51601		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A	
PRODUCT DESCRIPTION			
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)		NDA 21-116	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) levothyroxine sodium tablets, USP		PROPRIETARY NAME (trade name) IF ANY Thyro-Tabs ®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) levothyroxine sodium, USP		CODE NAME (If any) N/A	
DOSAGE FORM: Immediate release tablets	STRENGTHS: 25, 50, 75, 100, 125, 150, 175, 200, 300 mcg	ROUTE OF ADMINISTRATION: Oral	
PROPOSED INDICATION(S) FOR USE: Hypothyroidism, Thyroid Goiter, Thyroid Cancer			
APPLICATION INFORMATION			
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: N/A Holder of Approved Application: N/A			
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER			
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA) N/A			
REASON FOR SUBMISSION Minutes of the teleconference of 15 June 2001 (Submission #16)			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED 1		THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.			
N/A			
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)			
N/A			

This application contains the following items: (Check all that apply)

1. Index	
2. Labeling (check one)	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))	
4. Chemistry section	
A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(f); 21 CFR 601.2)	
5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
15. Establishment description (21 CFR Part 600, if applicable)	
16. Debarment certification (FD&C Act 306 (k)(1))	
17. Field copy certification (21 CFR 314.50 (k)(3))	
18. User Fee Cover Sheet (Form FDA 3397)	
19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/> 20. OTHER (Specify) Lloyd, Inc. minutes of teleconference of 15 June 2001	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
 Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>W.E. Lloyd</i>	TYPED NAME AND TITLE W.E. Lloyd, DVM, PhD, Chairman, CEO	DATE 23 July 2001
ADDRESS (Street, City, State, and ZIP Code) 604 West Thomas Avenue, Shenandoah, Iowa 51601		Telephone Number (712) 246-4000

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 CSER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

Food and Drug Administration
 CDER, HFD-94
 12420 Parklawn Dr., Room 3046
 Rockville, MD 20852

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.

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission			
Information		Information	
NDA Number:	21-116 / N-132	Brand Name:	Thyro-Tabs®
OCBP Division (I, II, III):	DPE 2 - (HFD-870)	Generic Name:	Levothyroxine sodium
Clinical Division:	DMEDP - (HFD-510)	Drug Class:	Thyroxine
CPB Reviewer:	Steven B. Johnson, Pharm.D.	Indication(s):	Hormone replacement
CPB Team Leader:	Hae-Young Ahn, Ph.D.	Dosage Form:	Tablets
Submission Date:	05-OCT-2001	Dosing Regimen:	QD (once daily)
CPB Review Due Date:	01-NOV-2001	Route of Administration:	PO (oral)
Division Due Date:	NA	Sponsor:	Lloyd Inc.
PDUFA Date:	NA	Priority Classification:	NA

Clinical Pharmacology and Biopharmaceutics Information

Information Type	"X" if Included at filing	# of Studies Submitted	# of Studies Reviewed	Critical Comments (if any)
Table of Contents				
Tabular Listing of All Human Studies				
Human PK Summary				
Labeling				
Reference Bio- & Analytical Methods				
I. Clinical Pharmacology				
Mass Balance:				
Isozyme Characterization:				
Blood/Plasma Ratio:				
Plasma Protein Binding:				
Pharmacokinetics (PK) -				
- Healthy Volunteers -				
Single-Dose:				
Multiple-Dose:				
- Patients -				
Single-Dose:				
Multiple-Dose:				
Dose Proportionality -				
Single-Dose:				
Multiple-Dose:				
Drug-Drug Interaction Studies -				
In-vivo Effects ON Primary Drug:				
In-vivo Effects OF Primary Drug:				
In-vitro Studies:				
Subpopulation Studies -				
Ethnicity:				
Sex:				
Pediatrics:				
Geriatrics:				
Renal Impairment:				
Hepatic Impairment:				
Pharmacodynamics (PD) -				
Phase 2:				
Phase 3:				
PK / PD -				
Phase 1:				
Phase 2:				
Phase 3:				
Population Analyses -				
Rich Data Set:				
Sparse Data Set:				
II. Biopharmaceutics				
Absolute Bioavailability:				
Relative Bioavailability -				
Solution as Reference				
Other Formulation as Reference:				
Bioequivalence Studies -				
- Traditional Design -				
Single-Dose:				
Multiple-Dose:				

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

- Replicate Design -				
<i>Single-Dose:</i>				
<i>Multiple-Dose:</i>				
Food-Drug Interaction Studies:				
Dissolution:	X	X	X	
In-vitro/In-vivo Correlation:				
BCS Based Biowaiver Request:				
BCS Classification Information:				
III. Other CPB Studies				
Genotype / Phenotype Studies:				
Chronopharmacokinetics:				
Pediatric Development Plan:				
Literature References:				
TOTAL OF STUDIES		1	1	
Eligibility and QBR Comments				
Primary Reviewer Signature:			Date:	
Secondary Reviewer Signature:			Date:	
- Carbon Copy List (CC) -				
NDA	HFD-850	HFD-870	HFD-510	CDR
21-116		MALINOWSKI AHNH	MCCORTS	

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-116	Efficacy Supplement Type SE-	Supplement Number
Drug: Thyrotabs (levothyroxine sodium tablets, USP)		Applicant: Lloyd Inc.
RPM: Steve MccCort		HFD-510 Phone # 827-6415
Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
Application Classifications:		
<ul style="list-style-type: none"> <input type="checkbox"/> Review priority <input type="checkbox"/> Chem class (NDAs only) <input type="checkbox"/> Other (e.g., orphan, OTC) 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority 5S
User Fee Goal Dates		October 24, 2002
Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
User Fee Information		
<ul style="list-style-type: none"> <input type="checkbox"/> User Fee <input type="checkbox"/> User Fee waiver 		<input type="checkbox"/> Paid <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
<ul style="list-style-type: none"> <input type="checkbox"/> User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> <input type="checkbox"/> Applicant is on the AIP <input type="checkbox"/> This application is on the AIP <input type="checkbox"/> Exception for review (Center Director's memo) <input type="checkbox"/> OC clearance for approval 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
Patent		
<ul style="list-style-type: none"> <input type="checkbox"/> Information: Verify that patent information was submitted <input type="checkbox"/> Patent certification [505(b)(2) applications]: Verify type of certifications submitted 		<input checked="" type="checkbox"/> 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <input type="checkbox"/> For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). 		<input type="checkbox"/> Verified
Exclusivity Summary (approvals only)		X
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		NA

General Information

Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	X
• Reviews	X
Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
Outgoing correspondence (i.e., letters, E-mails, faxes)	X
Memoranda and Telecons	X
Minutes of Meetings	
• EOP2 meeting (indicate date)	NONE
• Pre-NDA meeting (indicate date)	X 10-14-98
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	X
Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X

Clinical and Summary Information

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X
Clinical review(s) (indicate date for each review)	X
Microbiology (efficacy) review(s) (indicate date for each review)	NA
Safety Update review(s) (indicate date or location if incorporated in another review)	NA
Pediatric Page(separate page for each indication addressing status of all age groups)	X
Statistical review(s) (indicate date for each review)	NA
Biopharmaceutical review(s) (indicate date for each review)	X
Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> Clinical studies 	X
<ul style="list-style-type: none"> Bioequivalence studies 	X

CMC Information

CMC review(s) (indicate date for each review)	X
Environmental Assessment	
<ul style="list-style-type: none"> Categorical Exclusion (indicate review date) 	X
<ul style="list-style-type: none"> Review & FONSI (indicate date of review) 	NA
<ul style="list-style-type: none"> Review & Environmental Impact Statement (indicate date of each review) 	NA
Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
Methods validation	() Completed () Requested (X) Not yet requested

Nonclinical Pharmacology Information

Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X
Nonclinical inspection review summary	NA
Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
CAC/ECAC report	NA



OFFICES OF DRUG EVALUATION
ORIGINAL NDA/ANDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 21-116

Drug: Thyrotabs® (levothyroxine sodium tablets) DATE 6-6-2000

Applicant Lloyd Inc. CSO McCort Phone (301) 827-6415

Regulatory Due Date: June 20, 2000

Arrange package in the following order:

Check or Comment

1. ACTION LETTER with supervisory signatures
Are there any Phase 4 commitments? AP AE NA
Yes No
2. Have all disciplines completed their reviews?
If no, what review(s) is/are still pending? Yes No
3. Completed copy of this CHECKLIST in package Chem/Ther Types 5S
4. LABELING (package insert and carton and container labels).
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)
Draft
Revised Draft
Final
5. PATENT INFORMATION
6. EXCLUSIVITY CHECKLIST
7. PEDIATRIC PAGE
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
If no audits were requested, include a memo explaining why.
10. REVIEWS:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	
GROUP LEADER'S MEMO	1 discipline, separate reviews	
MEDICAL REVIEW	with a sheet of colored paper.	pending
SAFETY UPDATE REVIEW	Any conflicts between reviews	N/A
STATISTICAL REVIEW	must have resolution documented	N/A
BIOPHARMACEUTICS REVIEW		x
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		x
- Statistical Review of Carcinogenicity Study(ies)		N/A
CAC Report/Minutes		N/A
CHEMISTRY REVIEW		pending
Labeling and Nomenclature Committee Review Memorandum		pending
Date EER completed <u>pending</u> (attach signed form or CIRT's printout)		OK <input type="checkbox"/> No <input type="checkbox"/>
FUR needed <u> </u> FUR requested <u> </u>		
Have the methods been validated?		Yes (attach) <input type="checkbox"/> No <input checked="" type="checkbox"/>
Environmental Assessment Review / FONSI Not needed (see memo)		Review <input checked="" type="checkbox"/> FONSI <input type="checkbox"/>
MICROBIOLOGY REVIEW		N/A
What is the status of the monograph?		N/A
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes
12. MINUTES OF MEETINGS
Date of End-of-Phase 2 Meeting NO MEETING
Date of pre-NDA Meeting 10-14-98
13. ADVISORY COMMITTEE MEETING MINUTES
or, if not available, 48-Hour Info Alert or pertinent section of transcript. Minutes Info Alert
Transcript No mtg
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS
15. If approval letter, has ADVERTISING MATERIAL been reviewed? Yes No
If no and this is an AP with draft labeling letter, has advertising material already been requested? Yes, documentation attached
No, included in AP ltr

ACTION PACKAGE CHECKLIST

- Page 2 -

16. INTEGRATED SUMMARY OF EFFECTIVENESS

_____ not needed _____

17. INTEGRATED SUMMARY OF SAFETY

_____ not needed _____

31 Draft Labeling Page(s) Withheld