

NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg,
0.088mg, 0.1mg, 0.122mg,
0.125mg, 0.15mg, 0.175mg,
0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Establishment Evaluation
Request

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 76187/000
Stamp: 06-JUN-2001
Regulatory Due:
Applicant: MYLAN PHARMS
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310
Priority:
Org Code: 600

Action Goal:
District Goal: 06-MAY-2002
Brand Name:
Estab. Name: LEVOTHYROXINE SODIUM
Generic Name:
Dosage Form: (TABLET)
Strength: ALL 11 STRENGTHS

Application Comment:
FDA Contacts: M. DILLAHUNT (HFD-613) 301-827-5848, Project Manager
M. SMELA JR (HFD-625) 301-827-5848, Team Leader

Overall Recommendation:
Establishment: _____

DMF No: _____ AADA:
Responsibilities: _____
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment: _____

DMF No: _____ AADA:
Responsibilities: _____
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment: 1110315
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310

DMF No: _____ AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment: _____

DMF No: _____ AADA:
Responsibilities: _____

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Profile: CTL

OAI Status: NONE

Estab. Comment:

<u>Milestone Name</u>	<u>Date</u>	<u>Req. Type</u>	<u>Insp. Date</u>	<u>Decision & Reason</u>	<u>Creator</u>
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

Establishment:

DMF No:

AADA:

Responsibilities:

Profile: CTL

OAI Status: NONE

Estab. Comment:

<u>Milestone Name</u>	<u>Date</u>	<u>Req. Type</u>	<u>Insp. Date</u>	<u>Decision & Reason</u>	<u>Creator</u>
SUBMITTED TO OC	11-JUL-2001				MIDDLETONS

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 76187/000**
Stamp: **06-JUN-2001** Regulatory Due:
Applicant: **MYLAN PHARMS**
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310

Priority:
Action Goal:
Brand Name:
Established Name: **LEVOTHYROXINE SODIUM**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **ALL 11 STRENGTHS**

Org Code: **600**
District Goal: **06-MAY-2002**

FDA Contacts: **M. DILLAHUNT (HFD-613)** **301-827-5848** , Project Manager
M. SMELA JR (HFD-625) **301-827-5848** , Team Leader

Overall Recommendation:

ACCEPTABLE on 01-AUG-2001 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: _____ DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

Establishment: _____ DMF No: _____
AADA No: _____

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: **1110315** DMF No:
MYLAN PHARMACEUTICALS INC AADA No:
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: _____

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-JUL-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: _____

Establishment: _____

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-AUG-2001
Decision: ~~ACCEPTABLE~~
Reason: DISTRICT RECOMMENDATION

Responsibilities: _____

2

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Reason:

b(4) Confidential Commercial Information

b(4) Trade Secret Information

b(5) Deliberative Process; Attorney- Client and
Attorney Work Product Privileges

b(6) Personal Privacy

b(7) Law Enforcement Records

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 76187/000**
Stamp: **06-JUN-2001** Regulatory Due:
Applicant: **MYLAN PHARMS**
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310

Priority: _____ Org Code: **600**
Action Goal: _____ District Goal: **06-MAY-2002**
Brand Name: _____
Established Name: **LEVOTHYROXINE SODIUM**
Generic Name: _____
Dosage Form: **TAB (TABLET)**
Strength: **ALL 11 STRENGTHS**

FDA Contacts: **M. DILLAHUNT (HFD-613)** 301-827-5848 , Project Manager
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 01-AUG-2001 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: _____

DMF No: _____
AADA No: _____

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

Establishment: _____

DMF No: _____
AADA No: _____

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: **1110315**
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310

DMF No: _____
AADA No: _____

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-JUL-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

NDA 76187

Levothyroxine Sodium
Tablets USP

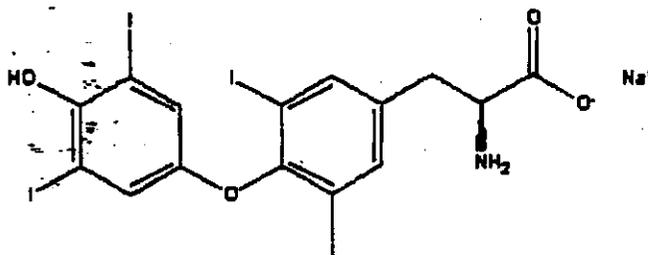
0.025mg, 0.05mg, 0.075mg,
0.088mg, 0.1mg, 0.122mg,
0.125mg, 0.15mg, 0.175mg,
0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Chemistry Review / CMC
Labeling Def Corresp

1. CHEMISTRY REVIEW NO. 1 (one)
2. ANDA # 76-187
3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26504-4310
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug for this ANDA is Unithroid® (Levothyroxine Sodium) Tablets manufactured by Jerome Stevens Pharmaceuticals, Inc. There are no patents that claim the listed drug referred to in this application. The referenced product is not covered by any exclusivity provisions.
5. SUPPLEMENT(s)
None
6. PROPRIETARY NAME
None
7. NONPROPRIETARY NAME
Levothyroxine Sodium Tablets USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Date of submission: June 5, 2001
10. PHARMACOLOGICAL CATEGORY
Levothyroxine is effective as replacement or supplement therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.
Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters.
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
NDA 21210 Jerome Stevens' Unithroid® tablets
13. DOSAGE FORM
Tablet
14. POTENCY
25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg

15. CHEMICAL NAME AND STRUCTURE



Levothyroxine sodium [25416-65-3]

Chemical name: L-Tyrosine-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-mono-sodium salt
Synonyms: L-3,3',5,5'-tetraiodothyronine, sodium salt (pentahydrate)

$C_{15}H_{10}I_4NNaO_4$

798.85607 (anhydrous)

16. RECORDS AND REPORTS

None

17. COMMENTS

This application is not approvable due to the deficiencies in the following areas.

(1) drug substance (2) analytical method

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable.

19. REVIEWER:
Liang-Lii Huang, Ph.D.
Endorsed by James Fan

DATE COMPLETED:
10/11/01;11/5/01
10/11/01;11/5/01

22

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Reason:

b(4) Confidential Commercial Information

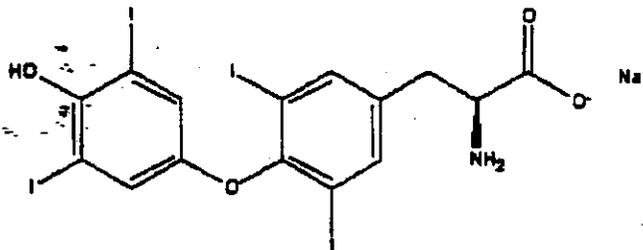
b(4) Trade Secret Information

b(5) Deliberative Process; Attorney- Client and
Attorney Work Product Privileges

b(6) Personal Privacy

b(7) Law Enforcement Records

1. CHEMISTRY REVIEW NO. 2 (two)
2. ANDA # 76-187
3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
4. LEGAL BASIS FOR SUBMISSION
The reference listed drug for this ANDA is Unithroid® (Levothyroxine Sodium) Tablets manufactured by Jerome Stevens Pharmaceuticals, Inc. There are no patents that claim the listed drug referred to in this application. The referenced product is not covered by any exclusivity provisions.
5. SUPPLEMENT(s)
None
6. PROPRIETARY NAME
None
7. NONPROPRIETARY NAME
Levothyroxine Sodium Tablets USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Date of submission: June 5, 2001
Minor amendment: January 18, 2002
Telephone amendment: April 19, 2002
10. PHARMACOLOGICAL CATEGORY
Levothyroxine is effective as replacement or supplement therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.
Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters.
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
NDA 21210 Jerome Stevens' Unithroid® tablets
13. DOSAGE FORM
Tablet
14. POTENCY
25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg

15. CHEMICAL NAME AND STRUCTURE

Levothyroxine sodium [25416-65-3]

Chemical name: L-Tyrosine-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-mono-sodium salt

Synonyms: L-3,3',5,5'-tetraiodothyronine, sodium salt (pentahydrate)

$C_{15}H_{10}I_4NNaO_4$

798.85607 (anhydrous)

16. RECORDS AND REPORTS

None

17. COMMENTS

This application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approvable.

19. REVIEWER:

Liang-Lii Huang, Ph.D.
Endorsed by James Fan

DATE COMPLETED:

4/23/02
4/23/02

15

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Reason:

b(4) Confidential Commercial Information

b(4) Trade Secret Information

b(5) Deliberative Process; Attorney- Client and
Attorney Work Product Privileges

b(6) Personal Privacy

b(7) Law Enforcement Records



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 19, 2002

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA SUPPLEMENT

N/A

**TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)**

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG,
100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG
ANDA 76-187
RESPONSE TO AGENCY TELEPHONE CALL OF APRIL 18, 2002

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review. Reference is also made to an April 18, 2002 telephone conference held between Dr. Paul Schwartz, Mr. James Fan, Dr. Sarah Ho and Mr. Liang Lii Huang of your Office, and representatives from our firm pertaining to the review of this application. As agreed during the telephone conference, Mylan wishes to amend the application by revising the finished drug product stability specifications for related compounds as follows:

- Not More Than _____ Individual Known Impurities _____
- Not More Than _____ Other Individual Impurity _____
- Not More Than _____ Total Impurities (excluding Liothyronine sodium) _____

The drug product specifications and post-approval stability protocols have been revised to reflect the agreed upon stability specifications for related compounds. The revised specifications and stability protocols are provided in Attachments A and B, respectively.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, is also being forwarded to the FDA's Baltimore District Office.

This amendment, which was submitted via facsimile on the date noted above, is also submitted in duplicate hard copy via Federal Express mail. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talt for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn
Enclosures

RECEIVED

APR 22 2002

OGD / CDER

Department—Fax Numbers
Accounting (304) 599-2595
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406

Information Systems
Legal Services
Maintenance & Engineering
Medical Unit

(304) 285-6404
(800) 848-0463
(304) 598-5408
(304) 598-5411
(304) 598-5445

Purchasing
Quality Control
Research & Development
Sales & Marketing

(304) 598-5401
(304) 598-5407
(304) 285-6409
(304) 598-3232

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number 76-187
Date of Submission Jan. 18, 2002
Applicant Mylan Pharmaceuticals Inc.
Drug Name Levothyroxine Sodium Tablets USP
Strength(s) 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, 0.3 mg

FPL Approval Summary

Container Labels
 0.025 mg, 0.05 mg, 100s Submitted January 18, 2002 vol. 4.1blue
 0.075 mg, 0.088 mg,
 0.1 mg, 0.112 mg,
 0.125 mg, 0.15 mg,
 0.175 mg, 0.2 mg, 0.3 mg

Package Insert Labeling LVTX:R1 Submitted January 18, 2002 vol. 4.1
 Rev. Date Nov. 2001

BASIS OF APPROVAL:

- No Patent Data For NDA 21-210.

No Exclusivity Data For NDA 21-210.

Reference Listed Drug
 RLD on the 358(h) form Unithorid Tablets
 NDA Number 21-210
 RLD established name Levothyroxine sodium
 Firm Jerome Stevens Pharmaceuticals
 Currently approved PI S-001
 AP Date 8/21, 2000.

Note:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	

Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringes, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult, Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/ANDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/ANDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and data study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of NDA 21210/ S-001, JSP; Unithyroid, ; approved 8/21/01
2. Patent/ Exclusivities: no unexpired patents or exclusivity, firm file a paragraph PI
3. Storage Conditions:
NDA - 20-25 C (68-77 F) with excursion between 15-30 C (59-86 F)
ANDA - store at CRT
USP - None
4. Dispensing Recommendations:
NDA - none
ANDA - Dispense in a tight, light resistant container as defined in UDP. Using a child resistant closure.
USP - tight light resistant container
5. Scoring:
NDA - partial bisected.
ANDA - scored
USP - none
6. Product Line:
The innovator markets their product in bottles of 100s and 1000s
The applicant proposes to market their product in HDPE bottles of 100s with CRC.
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).
8. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 4441-4470 section VII (Volume 10.1) .
9. Mylan, at Morgantown, will perform all operations in the manufacturing package and labeling.

Date of Review: February 06, 2002

Date of January 18, 2002

Submission:

cc: ANDA: 76-187
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:firmsam/mylan/lets&revs/76187ep.L
Review

151
2/06/02
2/6/000



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 18, 2002

N/A

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT (CMC AND LABELING INFORMATION ENCLOSED)

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG,
100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG
ANDA 76-187
RESPONSE TO AGENCY CORRESPONDENCE DATED NOVEMBER 9, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Agency's November 9, 2001 correspondence pertaining to this application (provided in Attachment I). In response to the Agency's comments of November 9th, Mylan wishes to amend this application as follows.

A. DEFICIENCIES

FDA COMMENT 1: Please include D₁₀ or D₅₀ particle size specification in addition to the present limit for the Levothyroxine Sodium USP drug substance.

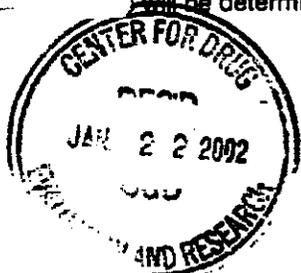
MYLAN RESPONSE: Mylan acknowledges the Agency's request for an additional particle size specification at the _____ level for the drug substance. Therefore, Mylan has revised the particle size specifications for the drug substance as follows:

_____ less than or equal to _____
_____ less than or equal to _____

The revised drug substance specifications are provided in Attachment A.

FDA COMMENT 2: Please indicate the method to be used for the moisture determination for the final _____ (pages 6626-6636).

MYLAN RESPONSE: The moisture content of _____ will be determined via _____



Handwritten signature/initials

G:\PROJECT\ANDA\LEVOTHYROXINE\AGENCY-LETTER-DATED-110901.doc		(304) 285-6404	Purchasing	(304) 598-5401
Department—Fax Numbers		(800) 848-0463	Quality Control	(304) 598-5407
Accounting	(304) 285-6403	(304) 598-5408	Research & Development	(304) 285-6409
Administration	(304) 599-7284	(304) 598-5411	Sales & Marketing	(304) 598-3232
Business Development	(304) 599-7284	(304) 598-5445		
Human Resources	(304) 598-5406			
	Information Systems			
	Label Control			
	Legal Services			
	Maintenance & Engineering			
	Medical Unit			

4

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Reason:

b(4) Confidential Commercial Information

b(4) Trade Secret Information

b(5) Deliberative Process; Attorney- Client and
Attorney Work Product Privileges

b(6) Personal Privacy

b(7) Law Enforcement Records

C. REGARDING LABELING DEFICIENCIES

MYLAN RESPONSE: Regarding the labeling deficiencies, Attachment L contains twelve (12) copies of the following final printed bottle labels and outsert for Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg.

BOTTLE LABELS

25mcg

Code RM1800A – Bottles of 100 Tablets

50mcg

Code RM1803A – Bottles of 100 Tablets

75mcg

Code RM1805A – Bottles of 100 Tablets

88mcg

Code RM1807A – Bottles of 100 Tablets

100mcg

Code RM1809A – Bottles of 100 Tablets

112mcg

Code RM1811A – Bottles of 100 Tablets

125mcg

Code RM1813A – Bottles of 100 Tablets

150mcg

Code RM1815A – Bottles of 100 Tablets

175mcg

Code RM1817A – Bottles of 100 Tablets

200mcg

Code RM1819A – Bottles of 100 Tablets

300mcg

Code RM1821A – Bottles of 100 Tablets

OUTSERT

Code LVTX:R1, Revised November 2001

The enclosed labeling incorporates the revisions requested in the Agency's letter of November 9, 2001. A copy of this correspondence is provided in Attachment I for the convenience of the reviewer.

Gary J. Buehler
Page 7 of 7

In order to facilitate the review of this labeling, Attachment J contains a side-by-side comparison of the final printed bottle labels to those draft bottle labels that were previously submitted and Attachment K contains a side-by-side comparison of the final printed outsert (LVTX:R1) to the draft outsert that was previously submitted. It is noted that prior to approval of this application, the Agency may find the color or other factors in the final printed labeling unacceptable and may request further changes to the labeling. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto *fs*

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosure

MINOR AMENDMENT

ANDA 76-187

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

NOV - 9 2001



TO: APPLICANT: Myland Pharmaceuticals Inc

TEL: 304-599-2595

ATTN: Frank R. Sisto

FAX: 304-285-6407

FROM: Sarah Ho

PROJECT MANAGER: 301-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

CMC and Labeling comments provided.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to 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 by mail at the above address.

MODE = MEMORY TRANSMISSION

START=NOV-09 14:30

END=NOV-09 14:31

FILE NO. =480

STN NO.	COMM.	ASBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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-CDER OGD DOC RM -

MINOR AMENDMENT

ANDA 76-187

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REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-187

Date of Submission: 6/5/01

Applicant's Name: Mylan Pharmaceuticals

Established Name: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, 0.3 mg

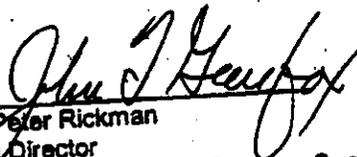
Labeling Deficiencies:

1. CONTAINER - 100s for each strength.
 - a. We acknowledge your comment that each product strength will have a unique color scheme.
 - b. Satisfactory in draft.
 - c. Ensure that the lot and expiration information are on the labels.
2. INSERT - Please make the following minor changes.
 - a. DESCRIPTION - changes "empirical" to "molecular".
 - b. PRECAUTION, Information for Patients, number 5 and number 12 - "...sodium tablet..." (note- add tablet)
 - c. DOSAGE AND ADMINISTRATION
 - i. General Principles, 2nd paragraph - revise to read "Levothyroxine sodium tablets" rather than "levothyroxine sodium". (Two occurrences)
 - ii. Pediatric Dosage, General Principles, 3rd paragraph - revise "teaspoons" to read teaspoonful.
 - iii. TSH Suppression in Well-differentiated Thyroid cancer and Thyroid Nodules, 1st paragraph - place "greater than" in bold print, as does the innovator.
 - d. HOW SUPPLIED - revise "capsule shaped" to read "caplet shaped".

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Fan, James M

From: Wu, Duu Gong
Sent: Thursday, October 18, 2001 1:28 PM
To: Fan, James M
Cc: Huang, Liang Lij; Lewis, David B; Chikhale, Elsbeth G
Subject: DMF review (DMF)

James:

Just to let you know that DMF update for levothyroxine has been reviewed. There are no issues as far as the acceptability of the updated CMC information. The firm did manufacture the DS _____ as described in the DMF. We intend to deal the dissolution issues that came with it with the drug product manufacturers through NDA/supplement reviews (when an individual firm uses the DS of _____). One problem with the DMF holder was that NDA holders have not been notified of the changes described in the DMF update. We will draft a letter to ask the DMF holder that the drug product manufacturers should be informed of any changes ASAP so that amendments/supplements can be submitted. Let me know if you have any question. If you want a copy of the review, please contact David Lewis or you can wait for the DMF and review to be sent back to the document room.

Duu-Gong

TELEFAX

2DA

specs

TO: Liang Lii Huang

OGD

FAX: 301-594-0180

PHONE: 301-827-5756

FROM: Elsbeth Chishale

Food and Drug Administration
Division of New Drug Chemistry II
5600 Fishers Lane, HFD-820
Rockville, Maryland 20857-1706

FAX: (301)827-0878

PHONE: (301)827-6420

DATE:

PAGES: _____ (Inclusive)

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Food and Drug Administration
Division of New Drug Chemistry II
5600 Fishers Lane- HFD-820
Rockville, Maryland 20857-1706

10-2-01

To: Liang Li Huang.

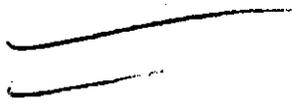
Sorry you had to wait for my reply for a few days, because yesterday I was moving to a new office & today I was unpacking, & my network was down so I could ~~not~~^{not} receive e-mails.

Anyway, enclosed is the information you requested, except for the drug substance that information is in the DMF — (review #1 & 2)

by David Lewis). Enclosed pages all come from my review. I will send you the review as an attachment via e-mail.

Please do not hesitate to call me with any questions.

Sincerely,



11
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