CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-402

Chemistry Review(s)

NDA 21-402

Synthroid® (Levothyroxine Sodium tablets, USP)

Abbott Laboratories

David B. Lewis, Ph.D.
Division of Endocrine and Metabolic Drug Products
(DMEDP, HFD-510)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-402

2. REVIEW Number: 1

3. REVIEW DATE: 22/07/02

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND —	06/06/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL NDA	31/07/01
AMENDMENT	12/09/01
AMENDMENT	22/03/02
AMENDMENT	03/05/02
AMENDMENT	15/04/02
AMENDMENT	23/05/02
AMENDMENT	24/05/02
AMENDMENT	31/05/02
AMENDMENT	27/06/02
AMENDMENT	11/07/02
AMENDMENT	12/07/02
AMENDMENT	18/07/02

- The amendment dated September 12th, 2001 provided 1-month stability data reports and minor corrections to CMC information.
- The amendment dated March 22nd, 2002 provided 6 month stability data results.
- The amendment dated April 15th, 2002 provided draft labeling.

- The amendment dated May 3rd, 2002 provided — assay data.
- The amendment dated May 23rd, 2002 provided revised draft labeling.
- The amendment dated May 24th, 2002 provided — assay data, statistics for supportive stability batches, a Phase 4 Commitment, and a revised stability commitment.
- The amendment dated May 31st, 2002 provided reference to a TeleCon between Abbott and the Agency, in which is was agreed to extend the review clock to 12 months. A tentative schedule for submitting updated stability data (potency & dissolution) was also provided.
- The amendment dated June 27th, 2002 provided — stability data (assay and some dissolution).
- The amendment dated July 11th, 2002 provided revisions to draft labeling.
- The amendment dated July 12th, 2002 provided — months stability data (dissolution) and a revision to the requested expiry.
- The amendment dated July 18th, 2002 provided a revised regulatory specification for the drug product (containing tightened dissolution tolerances).

7. NAME & ADDRESS OF APPLICANT:

Name:	Abbott Laboratories, Pharmaceutical Products Division
Address:	100 Abbott Park Road, D-491, APB6-1SW Abbott Park, Illinois 60064-3500
Representative:	Ernest Rivera, Regulatory Affairs Project Manager
Telephone:	(847) 937-7847 (Phone) (847) 937-8002 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Synthroid®
b) Non-Proprietary Name (USAN): Levothyroxine sodium tablets, USP
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) application; RLD is Unithroid® (levothyroxine sodium tablets, USP), 25 – 300 mcg tablets, NDA 21-210, Jerome Stevens Pharmaceuticals.

10. PHARMACOL. CATEGORY: Thyroid

Chemistry Review Data Sheet

11. DOSAGE FORM: Immediate release tablets

12. STRENGTH/POTENCY: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets

13. ROUTE OF ADMINISTRATION: Oral

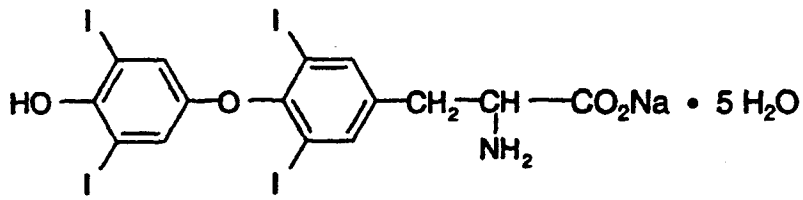
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

- Established (INN, USAN) Name: Levothyroxine sodium
- Inverted IUPAC Name: L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3',5'-diiodo-, monosodium salt, hydrate
- Molecular formula: $C_{15}H_{10}I_4NNaO_4 \cdot 5H_2O$
- Molecular weight: 798.86 g/mol (anhydrous material)
- Chemical structure:



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	7	N/A	N/A	Meets 21 CFR requirements for food contact safety
[redacted]	III	[redacted]	[redacted]	3	Adequate	03/02/01	Adequate [redacted]
[redacted]	III	[redacted]	[redacted]	3	Adequate	04/12/00	
[redacted]	I	[redacted]		2			Type I DMF-not reviewed
[redacted]	I	[redacted]		2			Type I DMF-not reviewed
[redacted]	III	[redacted]	[redacted]	3	Adequate	07/05/99	
[redacted]	III	[redacted]	[redacted]	3	Adequate	02/05/00	
[redacted]	III	[redacted]	[redacted]	3	Adequate	28/07/00	
[redacted]	III	[redacted]	[redacted]	3	Not adequate	26/11/99	See [redacted] section of review.
[redacted]	I	[redacted]	[redacted]	2			Type I DMF-not reviewed
[redacted]	I	[redacted]	[redacted]	2			Type I DMF-not reviewed

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

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

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	21/03/02	S. Ferguson
Pharm/Tox	Acceptable	23/04/02	K. Davis-Bruno, Ph.D.
Biopharm	Pending*		S. Johnson, Pharm.D.
LNC			
Methods Validation	Pending		
ODS	Acceptable	28/08/01	H-J. Kim, Pharm.D.
EA	Acceptable		D. Lewis, Ph.D.
Microbiology			

* According to a Memorandum to the NDA 21-402 Division file, "The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the data submitted in a facsimile sent to the Agency on July 12th, 2002, regarding the interim dissolution specification for SYNTHROID tablets. The interim specification of [redacted] % (Q) in 45 minutes is acceptable to the Agency". There are no other CMC-related issues in the (pending) Biopharmaceutics review; thus, this memorandum serves as Biopharm. Support for the CMC review of NDA 21-402.

The Chemistry Review for NDA 21-402

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The product is recommended for approval from the standpoint of chemistry, based on acceptable chemistry, manufacturing and controls (CMC) information and an acceptable cGMP status (based on product-specific cGMP inspections).

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

The sponsor has made a Phase 4 Commitment to develop an analytical method for the determination of impurities and degradation products in the drug substance and the drug product. The regulatory specifications (drug substance and drug product, release and shelf life) will be revised by adding a test for degradants and/or impurities and setting appropriate acceptance criteria (specified, unspecified, and total impurities). This commitment provides for its fulfillment within 1 year of approval of this NDA. This commitment was provided in the May 24th, 2002 amendment.

II. Summary of Chemistry Assessments

NDA 21-402 provides chemistry, manufacturing and controls (CMC) information for Synthroid® (levothyroxine sodium tablets, USP). The NDA was submitted in the CTD-Q format. Synthroid® has been marketed in the U.S. for almost 50 years without an approved NDA, and is one of the top ten prescribed drugs in the country. The presently marketed drug product contains an overage of levothyroxine sodium (T_4), and the proposed NDA product does not (targeted for 100% of labeled claim at release). The NDA tablet formulation is the same as the pre-NDA formulation, with the exception of the lack of overage.

A. Description of the Drug Product(s) and Drug Substance(s): The drug product has the proprietary name Synthroid® and the established name *levothyroxine sodium tablets, USP*. The dosage form is an immediate-release oral tablet, and is available in 12 strengths ranging from 25 to 300 mcg per tablet. The drug product is packaged in HDPE plastic bottles, aluminum-backed blister packs (unit dose containers), and professional (physician) samples, which are also packaged in blister packs.

The drug substance levothyroxine sodium, USP (T_4) is manufactured in-house at two different Abbott facilities (Kingstree, SC and Wyandotte, MI). The manufacturing processes at Kingstree and Wyandotte are similar, but differ between facilities. Bulk T_4 meets the requirements of the current USP monograph, but the sponsor utilizes

similar, but different analytical methods for potency assay and liothyronine (T_3) determination. Stability data is available for bulk T_4 as manufactured at Kingstree and Wyandotte, as is stability data for drug product manufactured with T_4 sourced from both facilities. The acceptance and stability specifications for T_4 include testing for only identified impurity/degradant ; development of tests, methods, and acceptance criteria for other process impurities and/or degradants is pending (see **Phase 4 Commitment, Recommendation I. B.**, above). A retest period of is proposed for the drug substance, which is supported by accumulated stability data.

Synthroid® tablets are manufactured , and contain the following excipients: lactose•H_2O, confectioner's sugar, acacia, povidone, magnesium stearate, talc, and various FD&C or D&C Aluminum Lake Dyes. All of the excipients are USP/NF compendial, and all of the coloring principles comply with current 21 CFR regulations. The only other manufacturing aid The manufacturing process and batch formula has not changed for over ten years. The was reduced for this NDA and the NDA product [Registry Lots] is manufactured using a variable manufacturing overage, ranging from , depending on tablet strength). The stability of Synthroid® tablets was evaluated using a reduced stability design (bracketed stability approach), in which the extremes of the strength range were stability-tested for each package presentation; one intermediate tablet strength (100-mcg) was also tested. The original NDA contained less than the recommended ICH stability data set, and the amount of stability data available upon completion of the review cycle was less than the requested expiry for the drug product. The firm also submitted supportive stability data for the currently marketed product (containing an overage); this data set included over 200 stability studies (all strengths and package presentations). In the assignment of expiry, the supportive stability data was also reviewed. The firm has made a Phase 4 Commitment to add tests and acceptance criteria for individual degradation products to the stability protocol within 1 year of NDA approval.

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

The typical dose of Synthroid® ranges from 12.5 to 200 mcg, to be administered once daily. Levothyroxine sodium has a narrow therapeutic index, and the correct dose is tailored to the individual patient, and is typically re-evaluated 1-2 times per year. The proposed tablet strengths are 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg per tablet. The proposed expiry is 10 months (all strengths packaged in 1000-count bottles and unit-dose blister packs) and 9 months (all strengths packaged in 100-count bottles) with storage at room temperature (25°C with excursions permitted between 15 and 30°C). The tentative expiry is supported by 10.5 months of ICH long-term stability data (25°C and 60% RY), 9 months of associated ICH intermediate stability data (30°C and 60% RH), and supportive stability data, which was obtained on the pre-NDA product

(containing an overage). The supportive stability data was accumulated under ICH conditions of long-term stability (25°C and 60% RH), and includes test results for over 50 lots of the pre-NDA product. The proposed tentative expiry is supported by full-time (10.5 months) acceptable long-term ICH stability data (25°C ± 2°C/60% RH ± 5% RH) and 9 months of ICH intermediate stability data (30°C ± 2°C/60% RH ± 5% RH).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval with an expiry of 10 months (1000-count bottles and unit-dose containers) and 9 months (100-count bottles) on the basis of acceptable chemistry, manufacturing and controls (CMC) information regarding the manufacture and testing of the drug substance and the drug product.

III. Administrative

A. Reviewer's Signature

S

APPEARS THIS WAY
ON ORIGINAL

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

/s/

David Lewis
7/22/02 02:26:00 PM
CHEMIST
NC
Made the changes to the "Phase 4 Commitment" section of the executive summary.

Sheldon Markofsky
7/22/02 03:24:21 PM
CHEMIST

NDA 21-402: Synthroid® (levothyroxine sodium tablets, USP)

ONDC position, regarding fileability:

- The NDA is fileable, for the following reasons:

  - Presence of 1 month of ICH stability data (long-term and intermediate) for drug product which has been manufactured in accordance with the criteria set forth in the July, 2001 Guidance for Industry: *Levothyroxine Sodium Products*.
  - NDA product targeted for release at 100 % of label claim.
  - Primary stability batches released with a mean assay value of 101 % of label claim.
  - Sufficient lots to support the strength range of 25 to 300 mcg tablets (adequate stability bracket).
  - Sufficient lots to support all proposed package configurations.
  - All other CMC filing requirements have been met.

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

/s/

David Lewis
10/12/01 12:51:04 PM
CHEMIST
Official Memo to file NDA 21-402 outlining the ONDC rationale behind its support for the application's fileability.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-402

Synthroid (levothyroxine sodium tablets, USP)

Chemistry review addresses claim for categorical exclusions from environmental assessment requirement on page 93.

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21402/000
Org Code : 510
Priority : 5S

Sponsor: ABBOTT LABS
100 ABBOTT PARK RD D491 AP6B1SW
ABBOTT PARK, IL 600646108

Stamp Date : 01-AUG-2001
PDUFA Date : 01-JUN-2002
Action Goal :
District Goal: 02-APR-2002

Brand Name : SYNTHROID(LEVOTHYROXINE SODIUM USP)TABS
Estab. Name:
Generic Name: LEVOTHYROXINE SODIUM USP
Dosage Form: (TABLET)
Strength : 25 - 300 MCG PER TABLET

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

Overall Recommendation: ACCEPTABLE on 21-MAR-2002by S. FERGUSON(HFD-324) 301-827-0062

Establishment : CFN : 1038973 FEI : 1038973
ABBOTT LABORATORIES
HWY 52 NORTH
KINGSTREE, SC 29556
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-MAR-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1836595 FEI : 3003362712
ABBOTT LABORATORIES
1609 BIDDLE AVE LT4 PLANT BLDG 63
WYANDOTTE, MI 48192
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-OCT-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2650166 FEI : 2650166
ABBOTT LABORATORIES
RD 144 KM 2.6
JAYUYA, PR 00664
DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-OCT-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-JAN-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

APPEARS THIS WAY
ON ORIGINAL