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

NDA #: 21-210 **DATE REVIEWED:** 7/27/00

REVIEW #: 1 **REVIEWER:** Elsbeth G. Chikhale

SUBMISSION TYPE	DOCUMENT DATE
ORIGINAL	10/19/99
AMENDMENT	3/22/00
AMENDMENT	6/6/00
AMENDMENT	6/21/00
AMENDMENT	7/26/00

NAME & ADDRESS OF APPLICANT: Jerome Stevens Pharmaceuticals, Inc.
60 DaVinci Drive
Bohemia, New York 11716

DRUG PRODUCT NAME
Proprietary: [ ] Tablets
Established: Levothyroxine Sodium, USP
Code Name/#:
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION: Replacement of endogenous thyroxin in patients with hypothyroidism. A pituitary TSH suppressant, in treatment or prevention of various types of euthyroid goiters. A diagnostic agents in suppression tests to aid in the diagnosis of mild hyperthyroidism.

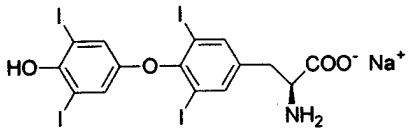
DOSAGE FORM: Tablet
STRENGTHS: 0.025, 0.050, 0.075, 0.088, 0.100, 0.112, 0.125, 0.150, 0.175, 0.200 and 0.300 mg

ROUTE OF ADMINISTRATION: Oral
Rx/OTC: x **Rx** _____ **OTC**

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

$C_{15}H_{10}I_4NNaO_4xH_2O$, Mol. Wt. 798.86 (anhydrous)

L-3,3^1,5,5^1-tetraiodothyronine sodium salt



REMARKS: NDA 21-210 is filled in response to a Federal Register Notice [FR 62(157),pp. 43535-43438], in which the FDA declared that drug products containing levothyroxine sodium are considered to be "new drugs" and need NDAs. The drug product has already been on the market for several years as an unapproved drug product. The drug substance, levothyroxine sodium, is manufactured by [ ]. Detailed information regarding the drug substance has been submitted as a Type II DMF by [ ]). A letter of authorization from [ ], dated 11-23-98, is enclosed. The DMF has been reviewed (chemist's review #1 and #2, dated 3-16-98 and 4-25-99 respectively, by D. Lewis of HFD-510). The information in the DMF was found adequate to support NDA [ ]. The two amendments, dated 3/22/00 and 6/6/00 contain updated long term stability data for the drug product. The third amendment, received 6/22/00 was for a change of the trade name from Unithriod® to [ ]. The final amendment faxed to the agency on 7/26/00 provided for responses to several information requests communicated to the applicant on 7/25/00. EERs were filed with the office of compliance for both the manufacturer of the drug substance [ ] and the manufacturer of the drug product (Jerome Stevens Pharmaceuticals) and the facilities were found acceptable on 12/28/99 and 2/7/00 respectively (see attached EES printout). An OPDRA consult for the trade name review was requested on 2/8/00 and again on 6/22/00 for the name change amendment. The first trade name review has been completed on 7/6/00 (see attached). An information request letter has been issued to one of the suppliers of [ ], based on the review of DMF [ ]. The response is pending. The applicant however, has withdrawn this supplier from the NDA in a faxed amendment dated 7/26/00.

CONCLUSIONS & RECOMMENDATIONS:

From chemistry standpoint, the NDA can be approved, if the labeling issues (trade name and storage statement) are resolved. See attached chemistry comments, regarding approved expiration dating and a chemistry phase IV commitment, to be included in the letter to the sponsor.

cc:
Org. NDA 21-210
HFD-510
HFD-510/EGChikhale/
HFD-510/DGWu/

Elsbeth G. Chikhale, Ph.D.
Review Chemist

R/D Init by:

Filename: 21210

SUPPORTING DOCUMENTS:

IND	[ ]
Sponsor	Jerome Stevens Pharmaceuticals Inc.
Letter date	11/5/98
CMC review date	12/8/98 by D. Lewis, Ph.D.
Conclusion of CMC review	Study may proceed

DMF #	Holder	Supplier of	Review date	Status
[		Levothyroxine sodium drug substance	3-16-98 4-25-99	Adequate
			8-15-96	Adequate
			8-6-99	Adequate
			7-22-99	Adequate
			12-5-99	Adequate
			6-8-00	*Deficient
			1-20-99	Adequate
			9-3-97	Adequate

*The applicant has withdrawn [ ] packaging as supplier on 7/26/00 in a amendment faxed to the Agency.

RELATED DOCUMENTS (if applicable):

CONSULTS: Trade name review consult requested on 2-8-00 for the name "Unithroid". After receiving an amendment with name change on 6/22/00, another name review consult was requested on 6/22/00 for the name "[ ]". The first consult was completed on 7/6/00 and the name "Unithroid" was found acceptable. The second consult review is pending.

Summary of Chemistry Review

A: Drug Substance: Satisfactory. See Chem. Rev. #1
B: Drug Product:
1. Components and Composition: Satisfactory. See Chem. Rev. #1.
2. Raw Material Controls: Satisfactory. See Chem. Rev. #1.
3. Manufacturer: Satisfactory. See Chem. Rev. #1.
4. Manufacturing and Packaging: Satisfactory. See Chem. Rev. #1.
5. Specifications and Analytical Methods: Satisfactory. See Chem. Rev. #1
Phase IV commitment to use dissolution test according to USP 24/NF 19 will be requested by Biopharm reviewer, Steven Johnson.
6. Containers: Satisfactory. See Chem. Rev. #1
7. Stability of Drug Product: Satisfactory. See Chem. Rev. #1. A phase IV commitment to develop test(s) to monitor degradation product(s) and to add the test(s) to the stability protocol within one year after approval, has been made. Degradation products over [ ]% will be identified.

C: Labeling: Satisfactory. See Chem. Rev. #1.

D: Enviromental Impact Analysis Report: Satisfactory. See Chem. Rev. #1.

E: Method validation: Satisfactory. See Chem. Rev. #17.

F: Establishment Inspection: Satisfactory. See Chem. Rev. #1.

Information requests and comments send by faxes: Chem. Rev. #18.

Comment to be included in letter to the sponsor: Chem. Rev. #1.

EER print out: Chem. Rev. #1.

Trade name consult: Chem. Rev. #1.