CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-301

CHEMISTRY REVIEW(S)

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

NDA #: 21-301

DATE REVIEWED: 5-08-01

REVIEW #: 1

REVIEWER: David B. Lewis, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	07-28-00	07-31-00	08-18-00
AMENDMENT	12-14-00	12-15-00	
AMENDMENT	02-27-01	02-28-01	
AMENDMENT	03-19-01	03-20-01	
AMENDMENT	04-06-01	04-09-01	
AMENDMENT	05-02-01	05-03-01	

NAME & ADDRESS OF APPLICANT:

Jones Pharma Incorporated
1945 Craig Road, PO Box 46903
St. Louis, MO 63146
(314) 576-6100 (Phone)
(314) 469-5749 (FAX)

DRUG PRODUCT NAME

Proprietary: Levoxyl® Tablets
Established: Levothyroxine Sodium Tablets, USP
Code Name/#:
Chem.Type/Ther.Class: 5S

PHARMACOL. CATEGORY/INDICATION: Treatment of hypothyroidism, thyroid goiter, and thyroid cancer

SPOTS: ___ YES _X_ NO

DOSAGE FORM: Solid Oral tablets

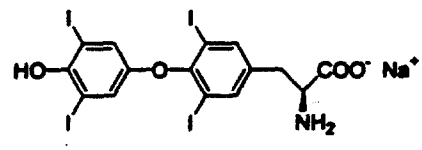
STRENGTHS: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: _X_ Rx __ OTC

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

Levothyroxine Sodium, USP $C_{15}H_{10}NI_4O_4Na \cdot xH_2O$ 798 g/mol



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

DMF's [redacted] are Type I packaging DMF's, and were not reviewed.

RELATED DOCUMENTS (if applicable):

Type/Number	Subject	Holder	Status	Review Date
DMF [redacted] Type II	Levothyroxine sodium	[redacted]	Adequate	4-29-99
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	5-07-99
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	9-10-99
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	9-28-98
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	5-12-99
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	5-02-00
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	3-21-01
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	9-01-97
DMF [redacted] Type III	[redacted]	[redacted]	Adequate*	10-29-99
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	3-21-01
DMF [redacted] Type III	[redacted]	[redacted]	Adequate**	7-25-00
DMF [redacted] Type III	[redacted]	[redacted]	Adequate	8-08-95

* Adequate for the [redacted] identical raw materials of fabrication)
** Adequate for [redacted] in general

CONSULTS: OPDRA

REMARKS: Jones Pharma Incorporated (JPI Jones) has filed NDA 21-301 in response to the Federal Register Notice dated 8-14-97 [62 FR 43535], which announced that drug products containing levothyroxine sodium (T_4) were to be classified as new drugs and were subject to FDA review. Jones Pharma has been marketing their T_4-containing drug product without an approved NDA under the trade name of Levoxyl® since the mid-1980's. The drug substance (levothyroxine sodium, USP) is manufactured by ——————————————— ; a LOA, allowing reference to Type II DMF —— dated 11-10-99, is provided. DMF —— has been reviewed and found adequate to support NDA's (CR's # 1 and 2, dated 3-16-98 and 4-29-99, respectively, D. Lewis, Ph.D., reviewer). The drug product is manufactured by JMI-Daniels Pharmaceuticals, Inc. (St. Petersburg, FL), which is a wholly owned subsidiary of Jones Pharma. The drug product is packaged in bottles —— 100-, and 1000-count), and in unit dose containers (10-tablet strips and 7-tablet cards [physician samples]). The drug product is manufactured with a target levothyroxine sodium content of 100 % of label claim; evaluation of the finished product COA's indicate that the actual overage (excess) of drug substance at release is negligible. The primary stability data, which was submitted in support of this application, utilized a reduced stability design (stability bracket). The particular stability bracket proposed by the sponsor is more extensive than the bracketing plan suggested by the Agency. Stability samples were stored under ICH conditions of long-term, intermediate, and accelerated conditions. Acceptable stability data is provided out to 15 months (long-term storage conditions). The *amendment dated 12-14-00* provides executed batch records for representative primary stability lots, two LOA's allowing reference to Type III packaging DMF's, and updated stability data. The *amendment dated 2-27-01* provides more updated stability data. The *amendment dated 3-19-01* provides a patent certification. The *amendment dated 4-06-01* provides updated stability data and statistical analysis of the assay regression (projected losses of potency). The *amendment dated 5-02-01* provides updated stability data. An EES report, dated 10-16-00, regarding the pertinent facilities for this NDA (manufacturing sites for the drug substance & drug product, along with the testing facilities, and the packaging site for unit-dose containers) is attached (acceptable). Draft labeling is provided (Package Insert and labels for the immediate containers and container cartons). The OPDRA consult voiced no objections to the proposed trade name Levoxyl®.

CONCLUSIONS & RECOMMENDATIONS: Adequate information has been provided regarding chemistry, manufacturing and controls. The application is approvable from the standpoint of chemistry.

cc:
Org.
HFD-510/Division File
HFD-820/Chemist/D. Lewis/DG Wu
HFD-510/S. McCort

———————

David B. Lewis, Ph.D.
Review Chemist

R/D Init by:

Filename: ———————

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
5/9/01 08:00:22 AM
CHEMIST
Adequate information has been provided regarding CMC. From the standpo
int of chemistry, this application is approvable.
I made the last change. JMI-Daniels does perform full testing on levot
hyroxine sodium. I referenced the pages for the acceptance protocol, t
he COA, and the acceptance methods. This did not affect the pagination
. I cleaned up the chemical structures.

Duu-gong Wu
5/9/01 03:42:35 PM
CHEMIST