CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-301

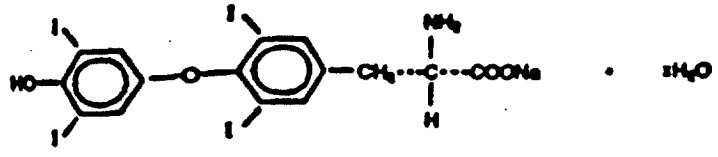
PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Key Words: Levothyroxine Sodium, hypothyroidism

Reviewer: Karen L. Davis-Bruno. Ph.D.; Supervisory Pharmacologist
Division of Metabolic and Endocrine Drug Products; HFD-510
Review Completion: 9/18/00
Review #1
Submission Date: 7/31/00

NDA 21-301
Information to the Sponsor: No
Sponsor: Jones Pharma Inc., St. Louis, MO
Manufacturer: JMI-Daniels Pharmaceuticals Inc., St. Petersburg, FL
DRUG:
Generic name: levothyroxine sodium tablets
Chemical name: O-(4-hydroxy-3,5,-diiodophenyl)-3,5,-diiodo-L-tyrosine monosodium
CAS number: 25416-65-3 [hydrate], 55-03-8 [anhydrous]
Molecular Formula/Molecular Weight: $C_{15}H_{10}I_4NNaO_4 \bullet x\ H_2O$; 798.86
Structure:



Relevant NDAs: NDA 21-210,

Drug Class: synthetic thyroid hormone

Indication: thyroid hormone replacement therapy

Clinical Formulation: tablets containing: 25, 50, 75, 88, 100, 112, 135, 137, 150, 175, 200 300 µg levothyroxine
Excipients: microcrystalline cellulose, NF; croscarmellose sodium, NF; Lake dyes containing a blend of D&C yellow #10 and D&C Red #30 to differentiate dosage; magnesium stearate, NF

Route of Administration: oral

Previous Clinical Experience: Extensive with many currently approved products see Related NDAs.

Introduction and Drug History: Levothyroxine has been marketed extensively for many years in both a tablet and injectable form. The indication is for replacement of thyroid hormone in hypothyroidism. Under a Federal Register notice of August 14, 1997 (volume 62, Number 157) current products will be branded mislabeled as of August 2001 in the absence of approved NDA and removed from the market. The prior lack of stability and batch to batch variability in these products as a class was the impetus for this legislation.

Studies Reviewed within this Submission: preclinical data was not submitted

OVERALL SUMMARY AND EVALUATION: Levothyroxine has been marketed extensively for many years. The indication for replacement of reduced naturally occurring thyroid hormone indicates little safety concern. Potential problems may arise from inappropriate dosing. Prior experience suggests that proper monitoring can minimize the associated safety risk.

Safety Evaluation: There are no preclinical safety issues with this product provided proper replacement dosing is performed with adequate monitoring and appropriate product stability is demonstrated.

Conclusions: Pharmacology recommends approval.

COMMUNICATIONS REVIEW:
Labeling Review: The draft labeling is adequate as proposed for the pharmacology sections.

RECOMMENDATIONS: none

/S/

Karen Davis-Bruno; Ph.D.
Supervisory Pharmacologist, DMEDP

Cc:HFD510/Davis-Bruno/Yang

APPEARS THIS WAY
ON ORIGINAL