

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Levothyroxine Sodium

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Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)

HFD#510

Review Completion Date: May 24, 2000

Review number: 1

NDA NUMBER: NDA 21-210

Serial number/date/type of submission: Initial NDA/ October 21, 1999

Information to sponsor: Yes (X) No () (class labeling)

Sponsor (or agent): Jerome Stevens Pharmaceuticals, Inc.; 60 DaVinci Drive; Bohemia, NY 11716

DRUG

Generic Name: levothyroxine, sodium tablets, USP

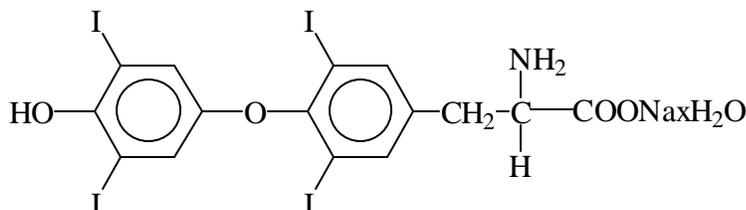
Trade Name: Unithroid7 Tablets

Chemical Name: Sodium L-3,3',5,5'-tetraiodothyronine (T₄)

CAS Registry Number: CAS-254-16-65-3 [hydrate]; CAS-55-03-8 [anhydrous]; CAS-51-48-9 [L-thyroxine]

Molecular Formula/ Molecular Weight: C₁₅H₁₀I₄NNaO₄xH₂O; 798.86

Structure:



Relevant INDs/NDAs/DMFs: None cited

Drug Class: synthetic thyroid hormone.

Indication: Replacement therapy for diminished or absent thyroid function.

Clinical formulation: Tablets available as 25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 : g Levothyroxine.

Exact formulation varies for each tablet due to amount of Levothyroxine[]. Inactive ingredients include:

Lactose, NF []

Microcrystalline Cellulose, NF []

Sodium Starch Glycolate, NF []

Magnesium Stearate, NF []

Colloidal Silicon dioxide, NF []

Each tablet size contains FD&C or D&C "Lake" dyes to clearly differentiate dosage.

Route of administration: Oral

Proposed clinical protocol or Use: Thyroid hormone replacement therapy. Dose is titrated. Tablets available as 25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 : g Levothyroxine.

Previous clinical experience: Extensive clinical use. Currently marketed as Levothroid Tablets (Forest), Levoxyl Tablets (Jones Medical Industries), Synthroid Injection and Synthroid Tablets (Knoll Pharmaceutical).

INTRODUCTION AND DRUG HISTORY: Levothyroxine has been marketed extensively for many years as both tablets and injection. The indication is for replacement therapy for diminished or absent thyroid function. One problem with currently marketed formulations is a lack of stability and batch to batch reliability. Under FR August 14, 1997 (volume 62, Number 157) it is defined that the current products will be branded as mislabeled in August of 2000 and removed from the market. Thus, there is need for a new NDA submission to provide for a continued source for therapy.

Studies reviewed within this submission: No preclinical data were submitted with this NDA. In pre-NDA discussions, it was indicated that the sponsor need only submit appropriate literature to cover labeling issues in the preclinical sections.

OVERALL SUMMARY AND EVALUATION:

Introduction: Levothyroxine has been marketed extensively for many years as both tablets and injection. The indication is for replacement therapy for diminished or absent thyroid function. For such replacement use with a naturally occurring essential hormone, there is little intrinsic risk. Potential problems may arise with inappropriate dosing. However, the extensive past human experience suggests that proper monitoring can keep this to a minimum.

Safety Evaluation: There are no preclinical safety issues with this product if proper replacement dosing is performed and stability of the product is appropriate.

Conclusions: Pharmacology recommends approval of this product. The Division has proposed that there be a class label for this product and recommendations for the preclinical sections are proposed below.

COMMUNICATION REVIEW:

Labeling Review (NDA):

Since there were no preclinical studies submitted and neither carcinogenicity, mutagenicity fertility nor reproduction studies have been performed, the preclinical sections do not require any specific animal data to be discussed and standard labeling as proposed in 21 CFR 201.57 are appropriate. There are several versions of labels listed in the appendix to this report for products already on the market, all of which are generally acceptable.

There is one issue this reviewer has with the pregnancy category. Some currently marketed versions refer to safety demonstrated in human studies and claim to be a category A. Actually, all currently marketed products list a pregnancy category A whether they refer to human data or not (see appendix for text of currently marketed products). This sponsor has not provided any reference to human data in the pharm/tox section of the NDA. Technically, in order for a product to be given a category A, there must be human data from well-controlled clinical trials. In addition, there are no animal data presented to support a category B (i.e., no findings in animal studies, no human studies performed) as defined by the CFR. With currently available

information, the pregnancy category should technically be category C. This may cause considerable confusion for several reasons:

1. Since long-time past labeling used category A, a switch to category C might imply that the newly approved products are somehow less safe than the currently marketed products when, indeed, they should be safer given stability considerations.
2. Current clinical practice is to maintain dosing of thyroid hormone during pregnancy. Current labeling for all products recommends that there be monitoring to prevent hypothyroidism in pregnant women. Such practice would seem at odds with a category C listing. This reviewer believes it is necessary to include information on current accepted practice in the label.
3. A category C listing might suggest to some patients that they should discontinue dosing during pregnancy. This would not be appropriate according to current clinical practice.

Based on current clinical practice and the above reasons, this reviewer believes that a category A is still appropriate even though this would be at variance with technical definitions listed in the CFR. The synthroid label has a rather extensive and (if supported by data) informative section on treatment during pregnancy. However, in the absence of human data presented by individual sponsors for the new NDA products, a more general approach to labeling is necessary. A class label for thyroid hormones is being developed by the Division. This reviewer recommends that the proposed wording of the class label for thyroxines be presented to the sponsor when it is completed.

RECOMMENDATIONS:

Internal comments: Pharmacology recommends approval of Unithroid⁷ Tablets. The Division has proposed that there be a class label for this product and this should be communicated to the sponsor when it is finalized by the Division.

External Recommendations (to sponsor): Communicate labeling as listed above.

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

Ronald W. Steigerwalt, Ph.D.
Supervisory Pharmacologist, DMEDP

PENDIX: CURRENT PRECLINICAL LABELING FOR PRODUCTS LISTED IN THE PDR

Forest Pharmaceuticals Levothyroid tablets:

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY--A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients on thyroid for established indications should not discontinue therapy. No confirmatory long-term studies in animals have been performed to evaluate carcinogenic potential, mutagenicity, or impairment of fertility in either males or females.

PREGNANCY-CATEGORY A--Thyroid hormones do not readily cross the placental barrier. The clinical experience to date does not indicate any adverse effect on fetuses when thyroid

hormones are administered to pregnant women. On the basis of current knowledge, thyroid replacement therapy to hypothyroid women should not be discontinued during pregnancy. NURSING MOTHERS--Minimal amounts of thyroid hormones are excreted in human milk. Thyroid is not associated with serious adverse reactions and does not have a known tumorigenic potential. However, caution should be exercised when thyroid is administered to a nursing woman.

Jones Medical Industries LevoxyI Tablets:

Carcinogenesis, Mutagenesis, and Impairment of Fertility-- A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients taking LEVOXYL for established indications should not discontinue therapy. There are no data suggesting that L-T₄ is mutagenic or impairs fertility; such studies in animals over the long term have not been performed.

Pregnancy--Category A-- Thyroid hormones do not readily cross the placental barrier. Clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women. On the basis of current knowledge, LEVOXYL replacement therapy to hypothyroid women should not be discontinued during pregnancy. During pregnancy, LEVOXYL requirements may increase; dosage should be guided pby periodic measurements of serum TSH concentration.

Nursing Mothers-- Some thyroid hormone is excreted in human milk but this is usually insufficient for hypothyroid nursing neonates. L-T₄ taken by nursing mothers is not associated with serious adverse reactions and does not have a known tumorigenic potential; properly indicated LEVOXYL therapy should be continued.

Knoll Pharmaceutical Co. Synthroid (same for tablets and injection)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic T₄ is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid hormone therapy and breast cancer has not been confirmed and patients receiving levothyroxine sodium for established indications should not discontinue therapy.

Pregnancy: Pregnancy Category A. Studies in pregnant women have not shown that levothyroxine sodium increases the risk of fetal abnormalities if administered during pregnancy. If levothyroxine sodium is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, levothyroxine sodium should be used during pregnancy only if clearly needed.

Thyroid hormones cross the placental barrier to some extent. T₄ levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of T₄ may not prevent *in utero* hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion and preeclampsia, and has been reported to have an adverse effect on fetal and childhood development. On the basis of current knowledge, SYNTHROID® (levothyroxine sodium, USP) should therefore not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T₄ concentrations may decrease and TSH concentrations may increase to values outside normal ranges. Postpartum values are similar to preconception values. Elevations in TSH may occur as early as 4 weeks gestation.

Pregnant women who are maintained on SYNTHROID should have their TSH measured periodically. An elevated TSH should be corrected by an increase in SYNTHROID dose. After pregnancy, the dose can be decreased to the optimal preconception dose.

Nursing Mothers: Minimal amounts of thyroid hormones are excreted in human milk. Thyroid hormones are not associated with serious adverse reactions and do not have known tumorigenic potential. While caution should be exercised when SYNTHROID is administered to a nursing woman, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.