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# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-137

# Pharmacology Review(s)

14-FEB-2000

# REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

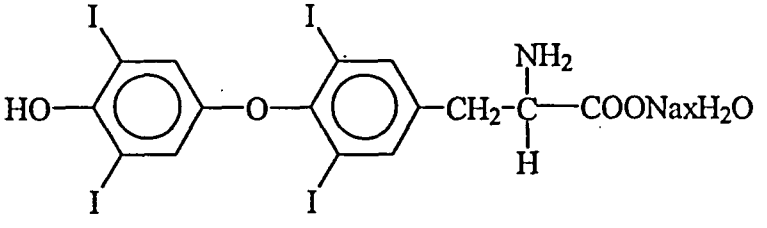
KEY WORDS: Levothyroxine Sodium

**Reviewer Name**: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader
**Division Name**: Division of Metabolic and Endocrine Drug Products (DMEDP)
**HFD#510**
**Review Completion Date**: February 14, 2000
**Review number**: 1

**NDA NUMBER: NDA 21-137**
**Serial number/date/type of submission**: Initial NDA/ May 3, 1999
**Information to sponsor**: Yes (X) No ( )
**Sponsor (or agent):** Vintage Pharmaceuticals, Inc.; 3241 Woodpark Blvd.; Charlotte, NC 28206

## DRUG

**Generic Name**: levothyroxine, sodium tablets, USP
**Trade Name**: LEVOLET
**Chemical Name**: Sodium L-3,3',5,5'-tetraiodothyronine ($T_4$)
**CAS Registry Number**: CAS-254-16-65-3 [hydrate]; CAS-55-03-8 [anhydrous]; CAS-51-48-9 [L-thyroxine]
**Molecular Formula/ Molecular Weight:** $C_{15}H_{10}I_4NNaO_4xH_2O$; 798.86
**Structure:**




**Relevant INDs/NDAs/DMFs**: IND —

**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, 137, 150, 175, 200 and 300 µg Levothyroxine.
Exact formulation varies for each tablet due to amount of Levothyroxine, cellulose and potassium iodide, but inactive ingredients include:
Microcrystalline Cellulose, NF —
Potassium Iodide —
Croscarmellose Sodium, NF —
Magnesium Stearate, NF —
Each tablet size contains FD&C or D&C 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, 137, 150, 175, 200 and 300 µg Levothyroxine.

**Previous clinical experience:** Extensive clinical use of active ingredient. Currently marketed as Levothroid Tablets (Forest), Levoxyl Tablets (Jones Medical Industries), Synthroid Injection and Synthroid Tablets (Knoll Pharmaceutical). This formulation is different from products currently on the market in that it contains potassium iodide —— which is not listed as a component of marketed products.

**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 Docket 97N-0314) 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. In meetings with the sponsor on October 14, 1994 and October 1, 1998, the FDA expressed concern that any product given NDA approval would serve as the standard for generics and thus should demonstrate good stability characteristics. This sponsor indicates that the patented product under consideration in this NDA has superior stability. Bioequivalence studies were performed with the various tablet sizes of the proposed product. Preclinical sections (carcinogenesis, mutagenesis, pregnancy, fertility) of the label must be addressed by provision of appropriate literature references.

**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 is a potential safety issue with this product regarding the inclusion of potassium iodide —— in the formulation. In the average patient, there should be little or no problem if proper replacement dosing is performed and stability of this product is appropriate. However, there could be very significant toxicities to the developing fetus in a pregnant woman due to the potassium iodide if high levels are administered. Although thyroid hormone is not likely to affect fetal development and current products recommend continuance of use during pregnancy, potassium iodide is likely to pass through the placenta in significant amounts and could cause fetal hypothyroidism due to feedback effects on the fetal thyroid function resulting in severe developmental defects. Available animal toxicity data in the literature suggest that these effects occur at very high doses. The lowest dose that this reviewer could find for potassium iodide having a developmental effect in animal reproductive toxicity studies was 100 mg/kg in rats. This was an abstract of a study (JY Lee, S Shoji, and Y Satow, Developmental Toxicity of Potassium Iodide In Rats Teratology 1989; 40(6):676-7). The reported NOEL in this study was 25 mg/kg (150 mg/m$^2$). This is considerably higher than

potential human exposure from LEVOLET (0.2 mg/m$^2$ for tablets containing 0.32 mg). The "safety margin" predicted by this study would be approximately 750 times the expected human exposure. The summary findings at the lowest effect level (100 mg/kg ~3000 X human exposure based on surface area comparisons) were post-implantation mortality, fetotoxicity and fetal death. It must be emphasized that this was not a complete study report. Other reported pregnancy findings in animals are at even higher doses. There is an additional study (T. Theodoropoulos, LE. Braverman and AG. Vagenakis Science 1979 205: 502-503-again, not a full toxicology report and also not a standard DART design) that demonstrated hypothyroidism in term rat fetuses and neonatal rats through postpartum day 10. Thyroid function returned to normal from postpartum day 18-60 even though iodide administration was continued during this period. The doses at which this occurred were 1 and 2 mg/rat. (If one uses a very conservative estimate of a 150 g adult rat instead of fetal rat weight, the safety margin is roughly 200 times the expected human exposure on a body surface area basis). A NOEL was NOT established in this study, however. No data were presented regarding developmental abnormalities in this study.

Based on these two rat studies, there should be relatively little risk at the proposed potassium iodide exposure in humans unless pharmacologic doses are reached. There are anecdotal reports of potassium iodide being linked to adverse pregnancy outcomes in humans. It is not clear what level of exposure to iodide was toxic. Ideally, the best preclinical information would come from a developmental and reproductive toxicology (DART) battery performed with the clinical formulation, but there are probably sufficient human data to allow for reasonable labeling precautions.

In a group discussion on February 14, 2000, it was indicated by the medical officer and the deputy division director that the amount of potassium iodide in this product poses little hazard to pregnant women. In the absence of preclinical data to support this conclusion, this product should be labeled category — as described in the CFR. One approach to help clarify this issue might be to conduct a DART battery with the clinical formulation to better establish a safety margin in animals, but it was decided at the meeting of February 14, that this was not necessary. An alternative approach would be for the sponsor to remove the potassium iodide from the formulation and demonstrate that the resulting product is stable.

Conclusions: Pharmacology recommends that LEVOLET is approvable (AE) pending acceptable labeling.
Recommendations for the preclinical sections of the label are proposed below.

**COMMUNICATION REVIEW:**

**Labeling Review (NDA):**
Since there were no preclinical studies submitted and neither carcinogenicty, mutagenicity fertility or 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 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 well-controlled human data. Technically, in order for a product to be given a

category A, there must be human data from well-controlled clinical trials. There also remains an unresolved concern regarding the potential effects of the potassium iodide in pregnant women. Therefore, this reviewer recommends a Category C for the pregnancy category.

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. The following label for the preclinical sections of levothyroxine products is proposed:

Additional comments to these sections could be added by the medical officer if sufficient information is available.

**RECOMMENDATIONS:**

Internal comments:

External Recommendations (to sponsor): Communicate labeling as listed below. (subject to additions/corrections by medical officer.)

**DRAFT LETTER CONTENT FOR SPONSOR:**

Labeling:

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:**

[

]

**Pregnancy: Pregnancy Category** [

]

**Nursing Mothers:** [

]

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

/S/

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

2/14/00

cc: NDA Arch
HFD510
HFD510/Steigerwalt/McCort/
Review Code: AE
Filename: 21137.catc.doc

APPEARS THIS WAY
ON ORIGINAL

## APPENDIX: 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 Levoxyl 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-$T_4$ 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 by 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-$T_4$ 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 $T_4$ 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. $T_4$ levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of $T_4$ 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 $T_4$ 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.

03-JUL-2001

# Memo

To: NDA 21-137
Drug: Levolet
Sponsor: Vintage Pharmaceuticals
From: Karen Davis-Bruno; Ph.D.; Supervisory Pharmacologist, HFD-510
Date: 7/3/01
Re: Pregnancy Category labeling comments

Levolet is a levothyroxine product containing potassium iodide (KI). The maximal dose of levothyroxine is a 0.3 mg tablet which contains 0.32 mg KI (0.2 mg/m$^2$). Potassium iodide is likely to cross the placenta in significant amounts during pregnancy resulting in fetal hypothyroidism and severe developmental defects. Iodine is effectively transferred to breast milk.

Published literature in rat[1] demonstrates fetal malformations (ventricular septal defects, right aortic arch, aberrant, subclavian arteries, incomplete lung, omphalocele and growth retardation) at doses ≥25 mg/kg/day (150 mg/m$^2$). This is the lowest dose noted in the literature and represents a 750X multiple of KI exposure compared to that in Levolet. A NOEL has not been established for fetal dysmorphogenesis with KI. Higher doses (100 mg/kg/day; 600 mg/m$^2$ ~3000X human exposure) results in fetal/neonatal mortality. An additional publication demonstrates fetal hypothyroidism in rat fetuses and neonatal rats given 1-2 mg/dam (13 mg/kg assuming 0.15 kg neonate weight, 80 mg/m$^2$)[2] through postpartum day 10. Iodide exposure levels in rats were ~400X that of Levolet, but not much different from the pharmacologic doses administered to humans of 150-880 mg/day (2.5 mg/kg, 93 mg/m$^2$ ). The maturation of the hypothalamic-pituitary –thyroid axis during postpartum week 1-2 in rat is analogous to human fetal function during gestation weeks 16-40[2]. Therefore there is reason to believe that the mechanism causing hypothyroidism in fetal/neonatal rat might also occur in humans.

Other products are approved for replacement therapy for hypothyroidism which lack potassium iodide and therefore do not have the safety concerns for pregnant women. Pregnancy category X is indicated if studies in animals or humans have demonstrated abnormalities or if there is positive evidence of a fetal risk based on adverse reaction reports from investigational or marketing experience and the risk of use in pregnant women clearly outweighs any possible benefit (e.g. safer drugs or other forms of therapy are available).

Recommendation To The Sponsor:

Please revise your label as follows:

Pregnancy Category X See "Contraindications section": Levolet may cause fetal harm when administered to a pregnant woman. Non-iodine containing thyroid hormone preparations are recommended for use in pregnant women, women who may become pregnant or nursing mothers. Published literature indicates that potassium iodide ≥25 mg/kg/day (150 mg/m$^2$) in the pregnant rat results in fetal malformations (ventricular septal defects, right aortic arch, aberrant, subclavian arteries, incomplete lung, omphalocele and growth retardation), representing a 750X multiple of the potassium iodide exposure in Levolet based on surface area comparison (mg/m$^2$). No known no effect levels has been established. Higher doses (100 mg/kg/day; 600 mg/m$^2$ ~3000X human exposure) resulted in fetal/neonatal mortality.

if the patient becomes pregnant while taking this drug, the patient should be

Lactation:

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/s/
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Karen Davis-Bruno
7/3/01 03:29:09 PM
PHARMACOLOGIST

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