CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-292

MEDICAL REVIEW(S)

NDA # 21-292
Novothyrox (levothyroxine sodium tablets)
GenPharm, Inc.
Date of original NDA submission: June 27, 2000
Date of NDA resubmission: November 29, 2001
Date of review: May 28, 2002

Medical Team Leader review of NDA[1]

Administrative background
In the Federal Register (FR) of August 14, 1997, FDA announced that oral drug products containing levothyroxine sodium (T4) are considered new drugs and subject to the new drug requirements of the FFD&C Act. This declaration was based upon longstanding and repeated documentation of problems in product quality relating to lack of stability and variability in batch-to-batch potency. Such problems have occurred with many levothyroxine products across different manufacturers. These deficiencies in drug quality have the potential to cause serious health consequences to patients requiring chronic levothyroxine therapy. In normals, thyroid hormone levels are extremely tightly regulated, and patients may suffer significant short and long-term problems if plasma thyroid hormone concentrations are either too high or too low.

Because of the medical necessity of these products, manufacturers of levothyroxine-containing products were given 3 years, until August 14, 2000, to obtain NDA approval. This deadline was subsequently extended to August 14, 2001.

In the FR notice, manufacturers wishing to continue to market oral T4 products after August 14, 2001 were informed that an NDA, including 505(b)(2) applications, must contain literature references supporting the safety and effectiveness of LT4 for the proposed indications and acceptable data relating to chemistry, manufacturing, and controls. In addition, bioavailability and *in vitro* dissolution studies are required in order to establish that the product proposed for marketing is readily and consistently absorbed across the full dosage range proposed. In short, the approach to development of levothyroxine-containing new drug products relies on the fact that levothyroxine itself is the appropriate treatment for supplementation or replacement in patients with insufficient endogenous thyroid hormone and for suppression of TSH in patients with thyroid nodules or cancer. However, the approvability of an oral T4 drug product based on a judgment that the specific product is safe and effective depends upon demonstration by the sponsor of acceptable quality, quantity, and *in vitro* and *in vivo* performance. This is accomplished through submission and review of manufacturing information, data from stability studies, and the results of bioequivalence/bioavailability and dissolution studies.

[1] This review is based on a template established by Dr. David G. Orloff, Division Director of Division of Metabolic and Endocrine Drug Products

NDA 21-292 was submitted on June 27, 2000 with the clinical section in accordance with the August 1997 FR notice. The sections addressing chemistry, manufacturing, and stability, and bioavailability/bioequivalence and dissolution studies were also submitted in accordance with the Division guidance required for approval of levothyroxine-containing products. During the initial review of this NDA, the clinical data section was found to be acceptable; however, the original proposed names. [redacted] were not acceptable proprietary names. With this resubmission, the sponsor has proposed the proprietary names [redacted] nd Novothyrox. The chemistry review revealed deficiencies that resulted in the issuance of an approvable letter on May 4, 2001. These deficiencies included:

CMC

1. inadequate CMC data on the drug substance, DMF—
2. inadequate certification that the gelatin used in the formulation of the drug product met the conditions specified in the 1997 "Guidance for Industry: The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use."
3. Inadequate stability data from the production-scale batches
4. a requirement to change the identity test to conform with current USP monograph

Additional comments on CMC-related and biopharmaceutics-related issues were conveyed in the AE letter.

With this resubmission, the sponsor has adequately responded to all the terms of the May 4, 2001 AE letter. The following sections of this memo summarize the results of the reviews by discipline.

Clinical rationale

This is a 505(b)(2) application and contains no clinical data. The sponsor has provided extensive literature references supporting the safety and effectiveness of LT4 for its proposed uses. Dr. Temeck has reviewed these references and has completed her exhaustive independent review of the clinical literature addressing thyroid physiology, thyroid hormone action and metabolism, clinical states of thyroid hormone excess and deficiency, and on the clinical efficacy and safety of levothyroxine. In addition, she has summarized the available information on thyroxine dosage and administration in adults and children and on drug-drug and drug-disease interactions for thyroid hormone. Much of the aforementioned has been adequately incorporated or reflected in draft labeling for LT4 drug products that is appended to Dr. Temeck's review. A revised labeling template for the package insert for levothyroxine sodium tablets products was sent to the sponsor on May 9, 2002. In addition, a recommendation was made to the sponsor in this correspondence to change the colors of some of the tablet strengths displayed on their container and carton labels to reduce the possibility of medication errors.

Levothyroxine is an iodinated derivative of tyrosine and is the major product of the mammalian (including man) thyroid gland. While T4 is the most abundant circulating

thyroid hormone, activation of thyroid hormone receptors intracellularly requires enzymatic deiodination to T3 in the periphery. Thus, T3 is the major active thyroid hormone in the circulation. Thyroid hormones are essential for survival. Administration of T4 simply supplements or replaces endogenously synthesized T4. Levothyroxine is used to supplement patients with absent or diminished thyroid function due to a variety of causes. In addition, replacement doses of T4 will suppress the hypothalamic-pituitary-thyroid axis, resulting specifically in reduced circulating TSH, and is thus used in the therapy of goiter, thyroid nodules, and thyroid cancer, all potentially TSH dependent.

For the uses described above, T4 is safe and effective. Of critical clinical importance, though, is that dose must be titrated to optimum TSH and T4 blood levels in order to ensure effectiveness and to avoid consequences of over- or under-treatment. These include, among others, effects on growth and development, cardiovascular function, bone, reproductive function, cognitive and emotional state, and on glucose and lipid metabolism. Safe and effective titration requires availability of multiple dosage strengths that permit the full range of total daily dosages (e.g., 25-300 mcg) in increments of —— 12.5 mcg. This may be accomplished clinically by combined dosing using more than one dosage strength to render the total daily dose needed and may also involve splitting tablets (e.g., for 12.5 mcg increments, taking half a 25 mcg tablet one day and the other half the next).

Chemistry

The DMF was amended by the DMF holder and found to be adequate by Dr. David Lewis, chemistry reviewer.

The sponsor submitted a certificate of Analysis from the supplier of the gelatin used in the formulation of this drug product stating that the raw material source of the gelatin is —— . In addition, the manufacturer of the drug product, Merck KGaA, certifies that no material related to the risk of transmitting BSE was used in the production of this drug product. Dr. Lewis reviewed this information and found the response adequate.

Stability data were provided on several lots of the lowest (25 mcg), highest (300 mcg), and intermediate strengths (100 mcg) of the drug product (bracketed stability testing). The chemistry review of these data supports an expiry of 24 months when the drug product is stored at room temperature (25^0C) with the permissible excursion range of 15^0 to 30^0C.

The sponsor submitted a change to the identity test to conform with the current USP monograph and the finished drug product specification has been revised to include the thin layer chromotography ID test. This information was reviewed and deemed adequate by Dr. Lewis.

Clinical Pharmacology and Biopharmaceutics
The initial biopharm review of NDA 21-292 included a relative bioavailability study between two 300 mcg tablets and 600 mcg solution and two dosage form proportionality studies between 50 mcg and 100 mcg tablets and 100 mcg and 300 mcg tablets. The relative bioavailability study shows that the relative bioavailability of two 300 mcg tablets of the GenPharm drug product is 98.8% relative to 600 mcg oral solution of a reference levothryoxine product. The dosage form proportionality studies established proportionality between twelve 50 mcg tablets and six 100 mcg tablets and six 100 mcg tablets and two 300 mcg tablets.

An *in vitro* dissolution study was also reviewed with the original NDA submission and dissolution specifications were recommended to the sponsor in the May 4, 2001 AE letter. The sponsor has submitted a proposal to have two separate dissolution specifications for the 25 to 175 mcg tablet strengths and the 200 to 300 mcg tablet strengths that differ only in the latter group having a higher volume. This proposal was reviewed by Dr. Stephen Johnson from OCPB and found to be acceptable.

Data Integrity
The Division of Scientific Investigations conducted an audit of the analytical portions of the biovailability/bioequivalence studies and the data were found to be acceptable for Agency review.

Summary and conclusions
Levothyroxine is indicated for the treatment of thyroid deficiency states and for suppression of pituitary TSH secretion in goiter, nodular thyroid disease, and thyroid cancer. This does not imply that all (or indeed any) currently available levothyroxine-containing oral drug products are safe and effective. Indeed, because of instances of failure of available products to maintain potency through the expiration date, because of lot-to-lot inconsistencies in the amount of active ingredient present in tablets of the same nominal dosage strength, problems related to both safety and efficacy have arisen. Chronic underdosing with T4 as well as both acute and chronic overdosing with T4 can have serious health consequences. Thus, only high-quality T4-containing products will be both safe and effective. In addition, as different LT4 products are not necessarily interchangeable, it is further necessary that the available range of dosage strengths for any given product permit titration of daily dose in increments of ___ 12.5 mcg. In order to accomplish this, at a minimum, a 25 mcg dosage strength is required.

The current application contains adequate information to support the clinical use of LT4 for the proposed indications.

The recommendations of OCPB and DNDC are contained in their reviews. The data provided permit conclusions that Novothyrox tablets have equivalent bioavailability to T4 oral solution, that there is dosage-form equivalence across the range of tablet

strengths, and that [redacted] may be labeled with an expiry of 24 months across all 11 dosage strengths.

Recommendation
This NDA may be approved. The proposed product name, Novothyrox, is an acceptable proprietary name.

Mary H. Parks, M.D.
Deputy Director, DMEDP (HFD-510)
CDER/FDA

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
5/29/02 01:54:31 PM
MEDICAL OFFICER

David Orloff
5/31/02 12:18:07 PM
MEDICAL OFFICER

04.06.01

NDA: 21,292 Dates submitted: 6/27/00 and 8/9/00
Drug: ——— (Levothyroxine sodium tablets)
Dates received: 7/6/00 and 8/14/00
Sponsor: Genpharm Date reviewed: 3/21/01

MEDICAL OFFICER REVIEW

Cover Sheet:

Review Summary:

This NDA was submitted as a 505(b)(2) application in response to FDA's August 14, 1997 Federal Register Notice (FRN). This FRN declared oral levothyroxine sodium products new drugs due to variations in the stability and potency of a given dosage strength from batch-to-batch produced by a given manufacturer and across different manufacturers. This variability has resulted in numerous recalls due to release of subpotent or superpotent tablets with their attendant adverse clinical consequences.

This review summarizes in detail published literature relating to the safety and efficacy of levothyroxine sodium as replacement or supplemental therapy of hypothyroidism and to suppress TSH in the treatment of goiter, nodules and thyroid cancer. A levothyroxine labeling template has also been prepared by the Agency and is attached.

Recommended Regulatory Action:

Approval

Submit to the sponsor a copy of the levothyroxine sodium labeling template prepared by FDA.

Jean Temeck, M.D.

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Table of Contents:

19. Draft algorithm for pediatric formulations- appended

1. INTRODUCTION TO THE NDA:

The August 14, 1997 Federal Register Notice declared orally administered levothyroxine (T4) drug products new drugs. Levothyroxine sodium is a drug with a narrow therapeutic index, therefore, small differences in blood or target tissue concentrations may have adverse clinical consequences, affecting both the efficacy and the safety of the product.

Subtherapeutic drug concentrations will result in inadequate efficacy. Inadequate treatment of congenital hypothyroidism will adversely affect IQ and linear growth. Inadequate treatment of acquired hypothyroidism will also compromise the child's growth, affect pubertal development (usually delaying puberty) and may result in poor school performance (due to impaired concentration and slowed mentation). Inadequate treatment of hypothyroidism in adults may also adversely affect mentation (slowness of thought and memory loss) and may be associated with decreased cardiac contractility, hypercholesterolemia and infertility. In addition, there is an increased likelihood of miscarriage, stillbirth and premature delivery. Even if the pregnancy is successful, the growth of the fetus and subsequent growth and development of the child may be retarded. Inadequate suppression of TSH by levothyroxine in a patient with well-differentiated thyroid cancer, may stimulate thyroid tumor growth and growth of metastases.

Toxic blood levels may adversely affect the drug's safety profile. Overtreatment for long periods of time has been associated with premature craniosynostosis in infants and may adversely affect the tempo of brain maturation in children; psychomotor retardation has been reported with overtreatment. In addition overtreatment may accelerate the bone age and prematurely close the epiphyses, thereby compromising final adult height. In adults, overtreatment has adverse effects predominately on the heart and bone. Patients overtreated with levothyroxine may have increased heart rates and cardiac contractility as well as left ventricular hypertrophy and arrhythmias. Elderly patients have an increased risk of atrial fibrillation. In addition, long-term treatment with levothyroxine sodium has been associated with decreased bone mineral density, particularly in postmenopausal women receiving suppressive doses of L-T4.

Therefore, it is essential that drugs with a narrow therapeutic index demonstrate consistent potency and stability from lot to lot. It has been reported (Hennessey et al, Ann Int Med 105:11-15, 1986) that levothyroxine dosage guidelines have required revision over the years to reflect reformulation changes which have resulted in products with increased potency and bioavailability.

In conclusion, maintenance of a euthyroid state, with avoidance of both over- and undertreatment is critical to maintaining the health and well-being of the patient with hypothyroidism. This is best accomplished by having products with consistent potency and stability which is the purpose of the FDA's August 14, 1997 Federal Register Notice.

The FRN of August 14, 1997 required manufacturers of oral T4 products to perform 2 bioavailability studies. One of these studies was to establish bioequivalence between two 300 mcg T4 tablets and a 600 mcg dose of Levothyroxine sodium for injection administered orally. The second study was to establish bioequivalence between 3 dosage strengths (50 mcg, 100 mcg and 300 mcg), each administered as a 600 mcg dose.

Note: Genpharm has been marketing levothyroxine sodium tablets in a number of countries outside the U.S.

Proposed indications:

Levothyroxine sodium is currently used for the following indications:

Hypothyroidism- As replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: cretinism, myxedema, non-toxic goiter, subclinical hypothyroidism, and primary (thyroidal), secondary (pituitary) or tertiary (hypothalamic) hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total absence of the thyroid gland, or the effects of surgery, radiation or drugs, with or without the presence of goiter.

Pituitary TSH Suppression- In the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well differentiated thyroid cancer.

Dosage form and route of administration: tablets for oral administration

2. FINANCIAL DISCLOSURE AND EVALUATION OF SAFETY IN THE BIOAVAILABILITY STUDIES:

Genpharm has certified that they did not enter into any financial arrangements with ——— the PI for the following bioavailability studies, that would affect the outcome of these studies.

a. Study No. 436-99-263:

This bioavailability study was an open-label, single-dose, 2-period, randomized crossover comparing 300 ug Genpharm levothyroxine tablets (dose 2 x 300 ug= 600 ug) to a Levothyroxine oral solution (prepared from Levothyroxine Sodium for Injection) in normal volunteers. There were 11 adverse events reported in 9/24 subjects (note: two subjects reported AEs on both the tablets and oral solution). None of the AEs were serious. On the tablets, 5 AEs were reported by 5 subjects. Headache and first degree AV block on the 48 hour ECG each occurred in 2 subjects and tachycardia in 1 subject. On the solution, 6 AES were reported by 6 subjects. As with the tablets, headache and first degree AV block each occurred in 2 subjects and tachycardia in one. In addition, another subject reported lightheadedness and fainting spell on the solution. All 4 reports of headache were regarded as possibly related to the treatment administered as was one case each of tachycardia (on the tablets) and first degree AV block (on the solution). None of these AEs required treatment.

b. Study No. 436-99-264:

This was an open label, single-dose, 2-period, randomized crossover study to compare the dosage-form equivalence between the 50 ug and 100 ug strengths of Genpharm Levothyroxine Sodium tablets under fasting conditions in normal volunteers. The dose administered in crossover fashion was 12 x 50 ug tablets or 6 x 100 ug tablets. 10 AEs were reported in 5 subjects. One subject did not crossover to the second study period due to persistence of first degree AV block noted on the 48 hour ECG in Period I. Therefore, 26 subjects completed Period I and only 25 subjects completed Period II. On the 50 ug tablets, 8 AEs were reported by 4 subjects (one subject reported 5 AEs). These 8 AEs included one each of the following: cramping, loss of appetite, nausea, skin clammy, tired (note: these 5 AEs were reported by 1 subject), 1 event of multifocal VBP's and 2 events of first degree AV block on the 48 hour ECG. On the 100 ug tablets, one subject each reported first degree AV block on the 48 hour ECG and feeling faint/light-headed. Note that 1 subject reported first degree AV block on both the 50 and 100 ug tablets. 8 of the 10 AEs were rated as mild in severity. Only the clammy skin and feeling of faintness/light-headedness were rated as moderate in severity. None of these 10 AEs were regarded as serious. Only 4/10 AEs were regarded as "possibly" or "almost certainly" related to the study drug: cramping, loss of appetite and nausea which were all reported in 1 subject and first degree AV block in another subject. None of these 10 AEs were treated.

c. Study No. 436-99-277:

This was an open-label, single-dose, 2-period, randomized crossover, fasting bioavailability study of levothyroxine sodium 600 ug given in 300 ug (2 Genpharm tablets) versus 100 ug (6 Genpharm tablets) administered to healthy volunteers. 28 subjects completed Period I but only 27 in Period II as one subject was a "no show" for the second period. On the 100 ug tablets, 2 AEs were reported by 2 subjects: light-headedness regarded as possibly related to the treatment and first degree AV block regarded as unlikely related to the tablets. On the 300 ug tablets, one subject reported tiredness, dizziness and light-headedness which were considered unrelated to the tablets. All AES were rated as mild in severity, none were serious and none required treatment.

3. REGULATION OF THYROID HORMONE SECRETION:

TRH (thyrotropin-releasing hormone), a peptide consisting of 3 amino acids, is synthesized in the hypothalamus. It traverses the hypophyseal-portal circulation to the anterior pituitary where it stimulates the synthesis and release of the glycoprotein, TSH (thyrotropin). TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormone from the thyroid gland. Serum T4 and T3 levels exert a feedback effect on TSH secretion- a decrement in serum T3 and T4 levels results in an increase in TSH secretion, whereas supraphysiologic concentrations of thyroid hormone will suppress TSH release.

4.THYROID HORMONE PRODUCTION, HALF-LIFE, BINDING TO PLASMA PROTEINS AND PLACENTAL TRANSFER:

T4 is produced solely by the thyroid gland. Approximately 80-100 ug of T4 is produced daily. However, the majority of T3 production (~80%) is derived from peripheral deiodination of T4 to T3, which occurs principally in the liver and kidney. The total daily production rate of T3 is 30-40 ug.

In euthyroid subjects, T4 has a half-life of 6-7 days; in hypothyroid patients, it is 9-10 days and in hyperthyroid patients, it is 3-4 days.

In euthyroid subjects, T3 has a half-life of ~1 day.

>99% of T4 and T3 is bound to plasma proteins. Therefore, <1% is in the "free" or unbound state. It is the free fraction which is biologically active.

Vulsma et al (NEJM 321(1):13-16, 1989) provided evidence to support the placental transfer of thyroid hormones.

5. REVIEW OF BASIC AND CLINICAL PHARMACOLOGY OF THYROID HORMONES:

Thyroid hormones are essential to activation of a multitude of metabolic processes essential for survival. They are also required for normal growth and development, and normal maturation of bone and the central nervous system.

5.A. Effects of thyroid hormones on metabolism:

Thyroid hormones accelerate the rate of cellular oxidation (respiration) by increasing uptake of oxygen by the mitochondria, enhancing the efficiency of oxidative phosphorylation and by increasing Na/K-dependent ATPase activity. There is a resultant increase in energy expenditure and heat production (i.e. thermogenesis or calorigenesis). Hence, thyroid hormones are the main controllers of the basal metabolic rate (BMR).

In addition, thyroid hormones stimulate gluconeogenesis and protein synthesis and play a role in the synthesis and degradation of lipids.

5.B. Effects of thyroid hormone on growth and development:

The protein anabolic effect of thyroid hormones is important in growth and development. The molecular mechanism for this effect is as follows: T4 or T3 enters the cell. T4 is converted to T3 by 5'-deiodinase activity. T3 then enters the nucleus where it binds to its specific receptor. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins.

5.C. Effects of thyroid hormones on maturation:

Thyroid hormones are required for normal maturation of bone and the central nervous system (CNS).

Mental retardation is a consequence of congenital thyroid hormone deficiency; deficiency during childhood may manifest as poor school performance.

Thyroid hormone is required for maturation and normal structural formation of the epiphyses. In children, thyroid hormone deficiency leads to epiphyseal dysplasia and delayed bone age. In adults, thyroid hormone directly stimulates osteoclasts to enhance bone resorption. Thyroid hormone excess may result in decreased bone mineral content and osteopenia.

5.D. Effects of thyroid hormones on target tissues:

The myocardium is an important target tissue for thyroid hormone action. Thyroid hormones exert a potent stimulatory effect on the myocardium, resulting in increased heart rate, cardiac contractility and cardiac output. This may be the result of: a). a direct stimulatory action of thyroid hormone on myocardial membrane Ca^{+2}-ATPase activity and b). a direct effect of thyroid hormone to increase the number of B-adrenergic receptors, thereby enhancing sensitivity of the myocardium to the effects of catecholamines.

The cardiovascular consequences of thyroid hormone excess include arrhythmias, angina, CHF and infarction.

6. PHARMACOKINETICS:

6.A. Absorption:

Absorption of orally administered T4 from the GI tract ranges from 42% to 80% in euthyroid subjects. The majority of the T4 dose is absorbed in the jejunum and upper ileum.

Various drugs and food may decrease T4 absorption, including: dilantin, propranolol, activated charcoal, bile acid sequestrants (colestipol and cholestyramine), aluminum hydroxide, ferrous sulfate, sucralfate, soybean infant formula, cottonseed meal and walnuts. It is prudent to advise patients to take their levothyroxine and other medications at different times.

Dietary fiber reduces the bioavailability of levothyroxine.

Fasting increases absorption of T4.

6.B. Distribution:

Thyroid hormones are rapidly distributed to the tissues and this is followed by a slow elimination phase.

Levothyroxine is almost completely bound to plasma proteins, only 0.05% exists as free thyroxine. ~80% of T4 is bound to TBG (thyroxine-binding globulin); lesser amounts are bound to TBPA (thyroxine-binding pre-albumin) and to albumin.

Thyroid hormones do not readily cross the placenta. There is no contraindication to breast feeding in mothers on thyroxine since minimal amounts of thyroid hormones are excreted in breast milk. However, excessive endogenous thyroxine may be secreted into milk in amounts sufficient to mask signs of hypothyroidism in the nursing infant.

6.C. Volume of distribution:

In Oppenheimer's study (JCEM 41:319, 1975), the volume of distribution in a 70 kg individual was 12.4 L (single compartmental) and 9.2 (noncompartmental) in normal and clinically euthyroid individuals with a history of hypothyroidism.

6.D. Metabolism:

The major pathway of thyroid hormone metabolism in man is through sequential deiodination. Approximately 80-85% of T4 and 50% of T3 and rT3 are metabolized through deiodination. Deiodination occurs in the thyroid, liver, kidney, placenta and fibroblasts. Of the deiodination pathways, monodeiodination is the most important and accounts for ~80% of the disposal of T4.

Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates. Glucuronidation is mediated primarily by hepatic microsomal enzymes with presumed direct biliary excretion. The sulfate conjugates of T4 and T3 are also secreted into the bile. Glucuronide conjugates are composed predominately of T4 and rT3, while the sulfate conjugates are predominately T3.

6.E. Elimination:

Thyroid hormones are eliminated predominately by the kidneys. Urinary excretion of T4 decreases with age.

~20% of thyroid hormones are excreted in the feces.

In addition, the intestinal bacteria can hydrolyze glucuronides and sulfates, thus facilitating reabsorption.

7. INDICATIONS AND USAGE:

Levothyroxine sodium is currently used for the following indications:

Hypothyroidism- As replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary) or tertiary (hypothalamic) hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total absence of the thyroid gland, or the effects of surgery, radiation or drugs, with or without the presence of goiter.

Pituitary TSH Suppression- In the treatment or prevention of various types of euthyroid goiters (See PRECAUTIONS), including thyroid nodules (See PRECAUTIONS), subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well differentiated thyroid cancer.

Toft (Clin Endocrinol 34:103-105, 1991) has listed some situations where hypothyroidism is present but replacement therapy with levothyroxine may not be necessary because the patient is asymptomatic or the hypothyroidism is transient: subacute thyroiditis (de Quervain's thyroiditis), postpartum thyroiditis, transient hypothyroidism following radioiodine or surgical treatment of Graves' disease, patients with Hashimoto's disease where excess iodine is implicated, neonates who have transplacentally received TSH-receptor blocking antibodies, individuals with inadequately treated Addison's disease, and increases in TSH during the recovery phase of non-thyroid illness.

8. CLINICAL SIGNS AND SYMPTOMS:

8.A. Hypothyroidism:

General:

Fatigue, weight gain, hypothermia, cold intolerance, myxedema fluid infiltration
of tissues;

CNS:

Mental retardation, memory and mental impairment, decreased concentration, depression, ataxia;

CV:

Bradycardia;

GI:

Constipation;

Dermatologic:

Dry skin, jaundice, coarseness or loss of hair;

Musculoskeletal:

Myalgias, muscle cramps;

Reproductive:

Irregular or heavy menses, infertility.

8.B. Hyperthyroidism or Overtreatment of Hypothyroidism:

General:

Fatigue, increased appetite, weight loss, heat intolerance, excessive sweating, dependent lower extremity edema;

CNS:

Hyperactivity, mental disturbances (emotional lability), nervousness, anxiety, irritability, sleep disturbances (insomnia),

CV:

Palpitations, tachycardia, arrhythmias (e.g. atrial fibrillation), heart failure;

Pulmonary:

Dyspnea

Ophthalmic:

Changes in vision (diplopia and blurring or loss of vision), photophobia, exophthalmos, lid retraction;

GI:

Frequent bowel movements;

Dermatologic:

Hair loss;

Musculoskeletal:

Tremor and muscle weakness;

Reproductive:

Decreased menstrual flow and impaired fertility.

Billewicz et al (Q J Med 28:255-66, 1969) developed a statistical approach to quantifying clinical signs of hyper and hypothyroidism in a way that they can be distinguished from a euthyroid state.

9. LABORATORY EVALUATION:

Diagnosis of hypothyroidism is confirmed by a sensitive TSH assay (second generation: sensitivity $\leq$0.1 mIU/L and, <0.01 mIU/L for third generation) and free T4. Adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. Serum TSH alone may be used (provided a sensitive TSH assay is used) to monitor therapy for primary (thyroidal) hypothyroidism because a linear inverse correlation exists between serum TSH and free T4. A sensitive TSH level is the best measure of occult over replacement. When clinically euthyroid patients exhibit an elevated TSH level, it may indicate inadequate T4 replacement, poor compliance or inadequate absorption.

However, serum TSH level is not a reliable indicator of the adequacy of replacement in secondary or tertiary hypothyroidism. In these latter conditions, it is necessary to monitor free T4.

Adequacy of replacement therapy for congenital and acquired pediatric hypothyroidism should be assessed by measuring both serum TSH and total or free T4.

10. DOSE REQUIREMENTS:

Because of its long half-life, the peak therapeutic effect with initial oral administration may not be achieved for 4-6 weeks and the duration of action after withdrawal is estimated to be between 2 and 4 weeks. A single daily dose is taken on an empty stomach.

10.A. Levothyroxine dose requirements in adults with hypothyroidism:

Fish et al (NEJM 316:764-770, 1987) reported that 112 $\pm$ 19 ug/day or 1.63 $\pm$ 0.42 ug/kg/day was the mean levothyroxine replacement dose. Carr (Clin Endocrinol 28:325-33, 1988) also reported 1.6 ug/kg/day as the optimal T4 replacement dose.

Munson (Principles of Pharmacology: Basic Concepts and Clinical Applications, 1996) recommends an initial dose of 100 ug/day in healthy young adults with dose increments of 25 ug every 4-6 weeks.

The following guidelines were proposed by the American Thyroid Association for the treatment of hypothyroidism in adults (Singer et al in JAMA 273:808-812, 1995):

- Adults with hypothyroidism require 1.7 ug/kg/day for full T4 replacement.
- Therapy is usually initiated in patients under the age of 50 years with full replacement.
- For patients older than 50 years or younger patients with a history of cardiac disease, an initial starting dose of 25-50 ug levothyroxine daily is recommended, with clinical and biochemical evaluations at 6-8 week intervals until the serum TSH level is normalized.
- Once the serum TSH level has normalized, visits every 6-12 months is sufficient, depending on the clinical situation. A physical examination should be performed annually and a serum TSH measured at least annually. For patients who have recently started receiving levothyroxine but their serum TSH has normalized, or who have had

their dosage, type or brand of thyroid preparation changed, the serum TSH concentration should be measured after 8-12 weeks.

- Some individuals older than 50 years, such as those recently treated for hyperthyroidism or those known to have had hypothyroidism for only a short time (such as a few months), may be treated with full replacement doses of levothyroxine.
- Pregnancy may increase levothyroxine requirements in hypothyroid patients. Serum TSH should be monitored during each trimester and appropriate adjustments made in levothyroxine dosage. The levothyroxine dosage should return to the prepregnancy dose immediately after delivery, and a serum TSH level should be obtained 6-8 weeks postpartum.
- If symptoms of palpitations, tremor, difficulty in concentrating, or chest pain are confirmed to be secondary to hyperthyroidism, levothyroxine therapy should be withheld for one week and restarted at a lower dose.
- Since levothyroxine overreplacement has been associated with reduced bone mineral content, particularly in postmenopausal women, it is recommended that these patients have their dose reduced until the TSH concentration is normalized, unless TSH suppression is the objective, as in patients with a history of well-differentiated thyroid cancer.
- Levothyroxine dosing should be spaced at least 4 hours apart from drugs that are known to interfere levothyroxine absorption from the gut, such as cholestyramine, ferrous sulfate, sucralfate and aluminum hydroxide antacids.
- Drugs that accelerate levothyroxine metabolism such as the anticonvulsants, phenytoin and carbamazepine and the antituberculous agent rifampin, may necessitate higher levothyroxine doses.

Brent and Larsen (Werner and Ingbar's The Thyroid, 7th edition, editors: Lewis Braverman and Robert Utiger, Lippincott-Raven Publishers, Philadelphia, 1996, chapter 77, pages 883-887), recommend that elderly patients receive no more than 50 ug levothyroxine/day, with dose increments of 25 ug at intervals of at least 6 weeks.

Toft, 1994; Munson, 1996 and Goodman and Gilman, 1996 recommend that patients with pre-existing cardiac disease start with 12.5-25 ug levothyroxine/day with increases of 12.5-25 ug every 6 weeks.

AHFS, 1998; Martindale, 1993 and Drug Evaluations, 1991, recommend that patients with severe hypothyroidism initiate levothyroxine therapy at 12.5-25 ug/day with increases of 25-50 ug q 2-4 weeks until the TSH is normalized.

Utiger (Endocrinology and Metabolism, editors Felig, Baxter and Frohman, third edition, McGraw-Hill, Inc., New York, 1995, Part III, Thyroid Disease, chapter 10, pages 435-553) and Falk both recommend an initial dose of 25 ug levothyroxine/day in those with a history of cardiac disease with incremental increases at intervals of at least 4-6 weeks as this is the period of time needed to elapse before the full effect of a given dose is realized (which is based on levothyroxine's long half-life).

Waldstein (Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy, ed. S. Falk, Raven Press, Ltd., New York, 1990, chapter 17,

pages 289-306), states that patients with profound or long-standing hypothyroidism may initiate levothyroxine therapy at 50 ug/day.

Becker (Principles and Practice of Endocrinology and Metabolism, ed. K. Becker, JB Lippincott Co., Philadelphia, 1990, chapter 47) recommends an initial levothyroxine dose of 12.5-25 ug/day in patients with severe hypothyroidism or in patients with underlying heart disease or in elderly patients. He states: "This low dose is recommended because an abrupt increase in metabolic rate and demand for increased cardiac output may precipitate angina, MI, CHF or arrhythmias. The dose may be increased by 25 ug every 4 weeks.

Williams (Textbook of Endocrinology, 8th edition, edited by Jean Wilson and Daniel Foster, WB Saunders Co., Philadelphia, 1992, section 3: Thyroid, chapter 8, pages 357-487) recommends that elderly patients with heart disease receive 12.5-25 ug levothyroxine/day with dose adjustments at 4-6 week intervals.

Mazzaferri et al (Am J Obstet Gyn 176:507-514, 1997) recommends a starting levothyroxine dose of 12.5-25 ug/day in patients with a history of cardiovascular disease or the frail elderly, with increments of 12.5-25 ug every 4 weeks until the target dose is achieved or symptoms develop.

De Groot (The Thyroid and Its Diseases, 6th edition, ed.: De Groot, Larsen and Hennemann, Churchill Livingstone Inc., New York, New York, 1996) recommends the following regimen for patients with cardiac disease or severe long-standing hypothyroidism: a starting dose of 25 ug levothyroxine/day with increments of 25 ug every 8 weeks until the serum TSH normalizes. He notes that patients with severe long-standing hypothyroidism may develop psychoses or agitation during the initial phase of levothyroxine replacement therapy, therefore, lower initial replacement doses are recommended. DeGroot also states that if a patient is taking what is thought to be a full replacement dose of levothyroxine, but the serum TSH is found to be elevated, the levothyroxine dose should be increased in 12.5-25 ug increments and the serum TSH repeated in 8 weeks.

Woeber (Arch Int Med 2000; 160:1067-1071) states that the mean replacement dose of L-T4 in adults is 1.6 mcg/kg/day. In patients with angina pectoris, L-T4 therapy should be initiated at doses of 25 mcg/day or less with dose increases at ~6 week intervals. Woeber makes the point that since it takes at least 4 weeks for TSH to stabilize in response to L-T4 therapy, dose adjustments should not be made more frequently.

The underlying cause of thyroid disease may influence the levothyroxine dose requirement (Brent and Larsen in Werner and Ingbar's The Thyroid- see reference above). For example, patients with primary hypothyroidism caused by chronic autoimmune thyroiditis require slightly higher doses of T4 than patients with Graves' disease who are hypothyroid as a result of radioiodine therapy (Bearcroft et al, Clin Endocrinol 34:115, 1991). Among those with Graves' disease, the T4 replacement

dose can vary as a function of not only the extent of antithyroid therapy but also the time since treatment. When levothyroxine is used to suppress TSH as in patients with thyroid cancer, the standard T4 suppressive dose is probably not less than 200 ug/day (Nilsson et al, Acta Med Scand 202:257, 1977). If subclinical hypothyroidism is treated, replacement levothyroxine doses generally range between 1.0-1.7 ug/kg/day. Per Mazzaferri (Am J Obstet Gynecol 176(3):507-514, 1997), the usual dose of levothyroxine for patients with subclinical hypothyroidism is 100 mcg/day. However, Mandel (Annals of Int Med 119(6):492-502, 1993 recommends a dose of 1 mcg/kg/day (50-75 mcg) levothyroxine to treat patients with subclinical hypothyroidism.

Pregnant women and obese patients may require higher than average T4 replacement doses (Mandel et al NEJM 323(2):91-96, 1990). The importance of treatment of maternal hypothyroidism even if mild is highlighted by Haddow et al, NEJM 341:549-555, 1999, to prevent an adverse effect on intellectual outcome in their offspring.

Surks (Treatment of Hypothyroidism in Werner and Ingbar's The Thyroid, 6th edition, ed. Braverman and Utiger, J.B. Lippincott Co., Philadelphia, 1991, pages 1099-1103) states that the criteria for appropriate T4 therapy in patients with secondary hypothyroidism are amelioration of the signs and symptoms of hypothyroidism and the restoration of serum T4 concentration to the upper half of the normal range.

Myxedema coma is a medical life-threatening emergency, and intravenous thyroid hormone replacement is recommended due to uncertain absorption of thyroid hormones from the gut (Goodman and Gilman, 1996, DeGroot 1996 and Williams, 1992).

DeGroot makes the point that in patients with central hypothyroidism (hypothalamic or pituitary hypothyroidism), a thorough endocrine evaluation should be performed to look for other hormone deficiencies (e.g. gonadotrophin and ACTH deficiencies). If ACTH deficiency is present, it is essential that glucocorticoid replacement therapy be initiated before thyroid hormone therapy so as not to precipitate an acute adrenal crisis (thyroid hormone accelerate the metabolic clearance of glucocorticoids and thus may precipitate an acute adrenal crisis if ACTH secretion is compromised).

Williams recommends the following regimen for withdrawal of thyroid hormone therapy when one wishes to determine the need for replacement therapy: reduce the levothyroxine dose by 50% and re-evaluate thyroid function in 6-8 weeks. If there is no significant increase in TSH level, withdraw levothyroxine completely and repeat blood tests 4-8 weeks later.

10.B. Levothyroxine dose requirements in pediatric patients:

The following guidelines were proposed by the American Academy of Pediatrics for the treatment of congenital hypothyroidism (Pediatrics 62:413-417, 1978 and Pediatrics 91:1203-1209, 1993):

- The average dose of levothyroxine at the start of treatment is 10-15 ug/kg/day with full replacement doses given to newborn infants.
- A lower starting dose of levothyroxine (e.g 25 ug/day) should be considered for infants with cardiac failure with an increase in dose in 4-6 weeks. Other adverse effects of levothyroxine such as hyperactivity in an older child can be minimized if the starting dose is one-fourth of the full replacement dose, and the dose in increased by one-fourth weekly until full replacement is reached.
- Infants with very low (<5 ug/dl) or undetectable serum T4 concentrations should begin to receive 50 ug daily.
- Secondary adrenal insufficiency must be considered when hypothyroidism is due to hypothalamic or pituitary disease. If adrenal insufficiency exists, glucocorticoid replacement should be initiated 2 days before T4 is started to avoid precipitating an acute adrenal crisis.
- The levothyroxine dose will need to be adjusted according to the infant's clinical response and determinations of serum T4 and TSH concentrations. The serum total T4 (corrected for variation in TBG levels) or free T4 should be maintained at all times in the upper half of the normal range and serum TSH suppressed into the normal range during the first 3 years of life. Some infants with congenital hypothyroidism, particularly in the early months of therapy, will have serum TSH levels in the 10-20 mU/L range (when it is optimal to maintain serum TSH below 10 mU/L), despite T4 levels in the upper half of the normal range. This elevated TSH appears to be the result of in utero hypothyroidism producing a resetting of the pituitary-thyroid feedback threshold. A failure of the serum T4 to increase into the upper half of the normal range by 2 weeks and/or the TSH to decrease below 20 mu/L within 4 weeks of initiation of levothyroxine administration, should alert the physician to the possibility that the child is not receiving adequate levothyroxine regularly. At this point, careful inquiry should be made regarding compliance, dose of medication and method of administration.
- Serum T4 and TSH should be monitored with the following frequency:
    a. at 2 and 4 weeks after the initiation of levothyroxine treatment
    b. every 1 to 2 months during the first year of life
    c. every 2 to 3 months between 1 and 3 years of age
    d. every 3 to 12 months thereafter until growth is completed
    e. at more frequent intervals when compliance is questioned or abnormal values are obtained.
    f. Serum T4 and TSH and physical exam, if indicated, should be performed 2 weeks after any change in levothyroxine dosage.
- The infant should be watched during the first 2 weeks of levothyroxine therapy for cardiac overload, arrhythmias, and aspiration from avid suckling.
- Routine clinical examination, including assessment of growth and development, should be performed at regular intervals.
- Overtreatment for long periods of time has been associated with premature craniosynostosis and may adversely affect the tempo of brain maturation (minimal brain damage has been reported in children with thyrotoxicosis during infancy). Overtreatment will also accelerate bone age.

- When permanence of thyroid disease is not established, levothyroxine administration should be discontinued for 30 days, at some point after the child is 3 years of age. At that time, serum T4 and TSH levels should be obtained. If the T4 is low and the TSH is high, permanent hypothyroidism is confirmed and therapy is reinstituted. If the T4 and TSH are normal, euthyroidism is assumed and a diagnosis of transient hypothyroidism is recorded. Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, one option when suspicion of permanence is high is to reduce the replacement dosage by half. If after 30 days, the serum TSH is elevated above 20 mU/L, the permanence of hypothyroidism is confirmed and full replacement therapy is resumed. However, if the serum TSH level has not risen, then treatment is discontinued for another 30 days with repeat serum T4 and TSH.

Serum T4 and TSH levels should be checked no sooner than 4 weeks after a levothyroxine dosage change since that period of time is necessary to reach steady state given the half-life of T4 (Rogers in American Family Physician 50:344-50, 1994).

Overtreatment may result in psychomotor retardation (Dubuis et al, JCEM 81:222-227, 1996).

Fisher (JCEM 72:523-529, 1991) makes the following points in his article:

a. an initial starting dose of 10-15 ug/kg/day of levothyroxine (or 50 ug/day in an average term infant of 3-4.5 kg), increases the serum T4 into the upper half of the normal range in 1-2 weeks. Serum TSH may be elevated above 20 mU/L despite serum T4 in the upper half of the normal range in some infants with congenital hypothyroidism (CH) particularly during the early months of treatment. This is due to a resetting in utero of the feedback threshold for T4 suppression of TSH release in infants with CH.
b. Therapy should be monitored, and individual T4 dose adjustments made, at 4-6 week intervals during the first 6 months, at 2-3 month intervals between 6-24 months of age, and at 3-6 month intervals thereafter. Assessments should include physical growth, motor development, bone maturation, and developmental progress at appropriate intervals. A Denver Developmental Screening Test or other screening tool may be useful to screen for developmental progress. More formal testing should be conducted when there is any suspicion of developmental delay and at 5-7 years of age.
c. When hypothyroidism is secondary to hypothalamic or pituitary disease, it is essential to look for other hormone deficiencies: e.g. growth hormone and ACTH deficiency.

Fisher makes the following additional points in another article (Fisher : Acquired Juvenile Hypothyroidism in Werner and

Ingbar's The Thyroid, 6th edition, ed. Braverman and Utiger, J.B. Lippincott Co., Philadelphia, 1991, pages 1228-1234):

a. The optimal maintenance dose for the treatment of acquired juvenile hypothyroidism is the dose that normalizes the serum TSH concentration and maintains the serum T4 in the midrange or upper range of normal for age, and that normalizes growth.
b. Excessive dosage results in accelerated bone maturation and premature craniosynostosis, at times accompanied by increased intracranial pressure and delayed neurological development.
c. Expected adult height may not be achieved in juvenile patients with prolonged hypothyroidism and marked growth retardation at the time of diagnosis and treatment. Decreased catch-up growth and eventual height reduction are likely if the untreated hypothyroid state exceeds 3 years in duration. Also, transient growth hormone deficiency occurs in 1% of patients with longstanding untreated hypothyroidism.

2 recent articles (Bongers-Schokking et al in J Peds 136:292-297, 2000 and Fisher J Peds 136:273-4, 2000) highlight the importance of early (<13 days of life), high-dose (T4 dose $\geq$ 9.5 mcg/kg/day) treatment of newborns with congenital hypothyroidism, especially those with severe CH, to prevent an adverse effect on intellectual outcome.

Martindale, 1993 and AHFS, 1998 recommend the following levothyroxine replacement dosage schedule:

0-6 months: 8-10 ug/kg/day
6-12 mos.: 6-8 "
1-5 yrs.: 5-6 "
6-12 yrs.: 4-5 "
>12 yrs.: 2-3 "

When growth & puberty are complete, the average levothyroxine dose is 1.6 or 1.7 ug/kg/day.

Drug Facts and Comparisons (publisher: Facts and Comparisons, St. Louis, MO, updated monthly, Thyroid Hormones, page 132i, © January 1995) cites the following levothyroxine replacement dosage schedule:

0-6 months: 8-10 mcg/kg/day
6-12 months: 6-8 "
1-5 years: 5-6 "
6-12 years: 4-5 "
> 12 years: 2-3 "

Sato et al (JCEM 44(3):553-9, 1977) studied 9 patients with athyreotic or ectopic cretinism, ages 6 months-17 years to examine the relationship between age and the dose of L-thyroxine to restore TSH to normal levels. The L-T4 dose which was associated with normal TSH responsiveness to TRH was high in infancy (10 ug/kg/day), decreasing with age to 3-4 mcg/kg/day in pubertal children. The adequate L-

T_4 dose between 4 and 12 years of age was 4-6 ug/kg/day. He concludes that these results suggest that the pituitary threshold for feedback regulation of TSH secretion by T_4 decreases with age in children with cretinism.

To minimize undesirable side effects (irritability, restlessness, decreased attention span and insomnia) in children with long-standing or severe hypothyroidism, Dallas and Foley (Pediatric Endocrinology, ed. Fima Lifshitz, third edition, Marcel Dekker, Inc., New York, New York, 1996, chapter 27, pages 391-99) recommend an initial dose of 25 ug levothyroxine/day with increments of 25 ug every 2-4 weeks until the desired effect is achieved.

11. DEMONSTRATION OF CLINICAL EFFECTIVENESS OF LEVOTHYROXINE:

The treatment of hypothyroidism with thyroid hormone replacement therapy dates back to 1891 when a case of hypothyroidism was treated by injecting an extract of sheep thyroid glands. This was followed in 1895 by demonstration that oral thyroid tissue was also effective and that the low metabolism and oxygen consumption of patients with hypothyroidism was due to atrophy of the thyroid gland. Dessicated thyroid was in use prior to the 1938 regulatory requirements to demonstrate efficacy and safety. Since thyroid hormone was the active ingredient in thyroid extract, when synthetic levothyroxine was introduced to the market in the 1950's, it was assumed to be "grandfathered" as well.

The majority of clinical studies in the literature have not been designed to demonstrate that levothyroxine is effective per se, but rather to define what best constitutes the optimal euthyroid state in terms of biochemical surrogate endpoints of thyroid function (TSH, total and free T4 and total and free T3), end organ physiologic effects (e.g. cardiovascular hemodynamic endpoints: left ventricular ejection fraction, cardiac output, systemic vascular resistance, etc.) and clinical outcome. Examples of well- controlled clinical efficacy studies include those by Cooper et al (Ann Int Med 101:18-24, 1984) and Monzani et al (Clin Invest 71:367-71, 1993) who demonstrated statistically significant improvement in the Billewicz Clinical Index, cardiac contractility and neuropsychological symptoms (e.g. memory impairment, anxiety, depression) in patients with subclinical hypothyroidism who were treated with levothyroxine compared to controls.

The efficacy of levothyroxine as suppressive therapy in the treatment of nontoxic nodular goiter was demonstrated by Miccoli et al (Surgery 114 (6):1097-1102, 1993). After a 3 year follow-up, significantly fewer recurrences after surgery occurred in patients receiving suppressive doses of levothyroxine (2.2- 3 mcg/kg/day) compared to those receiving substitutive doses (100 mcg/day). Hermus and Huysmans (NEJM 338(20):1438-1447, 1998) refer to other studies which examined the efficacy of levothyroxine suppressive therapy in patients with diffuse nontoxic goiters and nontoxic multinodular goiter.

The efficacy of levothyroxine in arresting the growth or in reducing the volume of benign solitary thyroid nodules was demonstrated by LaRosa et al (Annals of Internal Medicine 122(1):1-8, 1995). However, others (Gharib et al in NEJM 317:70-75, 1987 and Reverter et al in Clin Endocrinol 36:25-28, 1992) demonstrated no benefit.

Therefore, the value of thyroxine treatment in patients with benign solitary thyroid nodules is controversial (Hermus and Huysmans, NEJM 338(20):1438-1447, 1998).

Levothyroxine is unstable in the presence of light, temperature, air and humidity. Manufacturers have reformulated levothyroxine drug products over the years, and these reformulations may affect potency of the product. Hennessey et al (Annals Int Med 105:11-15, 1986) reported that the downward trend in levothyroxine replacement dose paralleled modifications in formulation with resultant increases in product potency and bioavailability.

12. SUMMARY OF SAFETY DATA:

12.A. Hypersensitivity reactions to levothyroxine products (probably to the dyes or tablet constituents) have been reported. The FDA has received several reports of hypersensitivity reactions including urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing.

12.B. Potential Adverse CNS Effects From Under- or Overtreatment:

See sections 10.A. and B. above in this review. In addition, pseudotumor cerebri has been reported in children receiving levothyroxine therapy.

12.C. End-organ effects:

There is a concern (Toft in Clin Endocrinol 34:103-105, 1991) that doses which produce TSH levels considered normal may produce increased end organ effects, such as nocturnal heart rate and sodium excretion.

12.D. Long-term Adverse Cardiovascular Effects:

(Note: an excellent recent review of the effects of thyroid hormone on the cardiovascular system is by Klein and Ojamaa in NEJM 344(7):501-9, 2001).

a. **Undertreatment:**

The heart may be affected by changes in serum thyroxine within the "normal" range in mildly hypothyroid patients as demonstrated by Ridgway (JCEM 53:1238-1242, 1981). Ridgway showed that patients with subclinical hypothyroidism may have decreased cardiac contractility.

There is an increased risk of coronary artery disease in patients with subclinical hypothyroidism (National Cholesterol Education Program Expert Panel, 1988). Also reported here was that hypercholesterolemia may be exaggerated in hypothyroid patients.

b. **Overtreatment:**

Sawin et al (Ann Int Med 100:641-645, 1984) reported variations in levothyroxine tablet content that affected TSH levels, an index of biologic activity. He stated that variations in tablet content and, therefore, potency, could be particularly hazardous to patients with coexisting coronary heart disease and hypothyroidism.

Sawin et al (NEJM 331:1249-1252, 1994) reported that elderly patients ($\geq$ 60 years) with low serum TSH due either to subclinical

hyperthyroidism or overtreatment with levothyroxine had ~3 fold increased incidence of atrial fibrillation over a 10 year period compared to those with normal TSH levels.

Forfar et al (Amer J Cardiol 44:9-12, 1979) reported that as many as 13% of patients with unexplained atrial fibrillation had biochemical evidence of hyperthyroidism.

Leese et al (Clin Endocrinol 37:500-503, 1992) concluded there was an increased risk of ischemic heart disease in hospitalized patients who had been taking levothyroxine compared to the general population. This risk was significant only for patients <65 years old but the risk was no different between those on L-T4 who had suppressed TSH levels and those on L-T4 with normal TSH levels.

Biondi et al (JCEM 77:334-338, 1993) reported the following cardiac abnormalities in patients on long-term thyroid hormone suppressive therapy: a statistically significant increase in heart rate and prevalence of atrial premature beats compared to normal age- and sex-matched control subjects. The echocardiogram showed a statistically increased LV mass index in the patient group. Furthermore, LV systolic function was enhanced, with higher values of fractional shortening and rate-adjusted velocity of shortening.2/20 patients on levothyroxine suppressive therapy had LV hypertrophy on ECG. The authors state that their findings of a significant correlation between the product of daily dose and treatment duration and LV mass index suggests that myocardial hypertrophy would be causally related to suppressive levothyroxine therapy.

In another study, Biondi et al (JCEM 78:1028-1033, 1994) again reported increased LV mass index in patients on levothyroxine suppressive therapy. This was associated with significantly enhanced systolic function.

Grund et al (Arch Int Med 149:921-924, 1989) reported that when subtle hyperthyroidism was corrected in patients on levothyroxine replacement therapy, there was a decrease in resting heart rate and LV ejection fraction.

Fazio et al (JCEM 80:7, 1995) reported that patients on long-term treatment with suppressive doses of levothyroxine show symptoms of impaired diastolic function. They noted an increase in LV mass and LV hypertrophy in the patients who showed signs of mild hyperthyroidism. It has been stated that this diastolic dysfunction may be a prelude to more serious limitations of cardiac function and physical performance (e.g. Bonow et al in Ann Int Med 117:502-510, 1992 reported that LV diastolic dysfunction may be a cause of CHF; Cuocolo et al in Circulation 81:978-986, 1990 reported LV hypertrophy in association with impaired diastolic filling).

Jennings et al (Br Med J 289:1645-1647, 1984) reported that a persistent elevation in free thyroxine level is associated with cardiac systolic time intervals in the thyrotoxic range in patients receiving levothyroxine replacement therapy for primary hypothyroidism. The cardiac systolic time intervals normalized and the serum T4 levels decreased when the levothyroxine dose was reduced.

Polikar et al (JACC 14:4, 1989) reported that levothyroxine replacement therapy is associated with an increase in basal, average and maximal heart rates.

Ching et al (Heart 75:363-8, 1996) reported that long-term suppressive L-T4 therapy (mean 9.6 yrs. with range of 3-21 yrs.) is associated with a statistically significant increase in LV mass index (18.4%) compared to normal controls.

Mercuro et al (JCEM 85(1):159-164, 2000) demonstrated the adverse effect of long-term suppressive therapy with levothyroxine on cardiac function and exercise capacity. 19 patients were receiving suppressive doses (1.8-4.0 mcg/kg/day) of levothyroxine post surgery for differentiated thyroid cancer or nontoxic goiter for a mean of 5.7 years (range: 2-20 years). Their cardiac function and exercise tolerance were compared to a control group of 19 healthy volunteers. In L-T_4-treated patients, intraventricular septum thickness, LV posterior wall thickness, end-diastolic dimension and LV mass index were significantly increased and exercise tolerance significantly decreased compared to the euthyroid controls. However, individual titration of the L-T_4 dose to the minimal amount necessary to suppress TSH, was associated with normalization of echocardiographic parameters and a significant increase in maximal workload in all 7 patients in which this was done.

The most frequently encountered severe complications of the thyrotoxic condition are tachyarrhythmias, thromboembolism and heart failure (Sawin et al, NEJM 331:1241-1252, 1994). Others (Proskey, 1977; Amikan and Riss, 1974; Kolter et al 1973; Cheah et al, 1972; Martinez-Rovira et al, 1969; Douglas et al, 1969; Barnett et al, 1967; Resnekov et al, 1977; Wei et al, 1979- see appended references), have reported myocardial infarction and coronary spasms with ventricular fibrillation in patients with thyrotoxicosis. Also, the frequency of atrial fibrillation also increases with age in those with hyperthyroidism (Forfar et al, Clin Endocrinol Metabol 14:491-508, 1985).

(Note: an excellent review article on the adverse effects of levothyroxine on the heart is by Haden et al in The Endocrinologist 6(4):322-327, 1996. Many of the above articles are summarized in this article. Woeber in Arch Int Med 2000; 160:1067-1071 refers to Ching's paper above and states that thyroid hormone excess may have adverse cardiac consequences).

12.E. Long-term Adverse Effects on Bone:

a. On Bone Mineral Density:

Franklyn et al (Lancet 340:9-13, 1992) showed no evidence of lower bone mineral density (at femoral and vertebral sites) in 49 patients (18 pre- and 26 post-menopausal women and 5 men) on long-term thyroxine therapy compared to controls. The treated patients had undergone subtotal thyroidectomy for well-differentiated thyroid cancer. Their mean $\pm$ S.D. thyroxine dose was 191 $\pm$ 50 mcg/day and the mean duration of therapy was 7.9 years (range 1-19 years). Also, no correlation was found between bone mineral density with thyroxine dose, duration of therapy, or with cumulative thyroxine intake or with tests of thyroid function.

Uzzan et al (JCEM 81:4278-9, 1996) performed a meta-analysis of all controlled cross-sectional studies of the effects of thyroid hormone therapy on bone mineral density that were published between 1982 and 1994. This analysis demonstrated substantial decreases (5-9%) in bone mineral density at the lumbar spine, the proximal femur, and the radius in post-menopausal women receiving long-term suppression therapy with thyroid hormone. No negative effect of therapy on bone mineral density was found in pre-menopausal women or in men.

Ross et al (Amer J Med 82:1167-1170, 1987) found a 9% decrement in forearm cortical bone density in 12/28 premenopausal patients who had been receiving levothyroxine therapy for $\geq$ 10 years. However, in the majority of these

patients, therapy was suppressive as judged by a high FT4I and a flat or subnormal TRH stimulation test.

Paul et al (JAMA 259:3137-3141, 1988) examined a group of 31 premenopausal women treated with L-T4 for at least 5 yrs., and found that, compared with control subjects, bone density was 12.8% lower at the femoral neck and 10.1% lower at the trochanter. ~55% of the patients (17/31) had suppressed serum TSH levels consistent with overreplacement. However, although the bone mineral densities at the femoral neck and trochanter sites were slightly less in the patients with suppressed TSH compared to patients with normal TSH on L-T4, the difference was not statistically significant. No significant correlation was found between thyroid function tests and axial bone density values.

Diamond et al (JCEM 72:1184-1188, 1991) reported that suppressive doses of T4 significantly reduce bone mineral measurements in both pre- and postmenopausal women with thyroid carcinoma.

Premenopausal women who were treated with a mean levothyroxine dose of 111 ug/day for 7.5 years had a decrease in bone mineral density at the femoral neck (-5.7%) and trochanter (-7.0%) sites, Ward's triangle (-10.6%), arms (~-8.0%) and pelvis (-4.9%) compared to age-matched controls (Kung et al JAMA 265:2688-91, 1991). Serum TSH levels were not suppressed. No correlation was found between the total body or regional BMD levels and the duration or dosage of L-T4 treatment or thyroid function results.

Stall et al (Ann Int Med 113:265-9, 1990) reported accelerated bone loss at the spine, hip and radius in 10 postmenopausal women overtreated with levothyroxine (low serum TSH levels) compared to normal controls. The mean duration of L-T4 therapy was 14.2 years. No significant correlation was found between the annualized rate of bone loss and the dose or duration of L-T4 therapy.

Greenspan et al (Amer J Med 91:5-13, 1991) provided supportive evidence that long-term levothyroxine therapy that maintains FT4I in the physiologic range is associated with a statistically significant, but clinically minimal, decrement in spinal and hip bone density in both pre- and postmenopausal women. The decrement at the hip was due to the inclusion of patients with treated Graves' disease.

Adlin et al (Amer J Med 90:360-366, 1991) reported that 19 postmenopausal women treated with levothyroxine for at least 5 years, had decreased bone mineral density of the femoral neck, Ward's triangle and trochanter compared to age-match controls. L-T4 treatment appeared to be supraphysiologic in 16/19 patients (84%) in whom serum TSH levels were low. (Note: mean T4 dose was 120 mcg/day and median T4 dose was 100 mcg/day). No correlation was found between thyroid hormone levels and bone density.

Roti et al (Endocrin Rev 14:401-423, 1993) have stated that most studies have not clearly indicated whether bone changes observed are a risk factor for developing clinically relevant osteoporosis and bone fractures, even though many have shown a clear relationship between thyroxine therapy and reduced bone mineral density.

Faber et al (Europ J of Endocrin 130:350-6, 1994) performed a meta-analysis of the results of 13 studies of bone density in several hundred women who were receiving long-term (5-15 years) T4 treatment, most of whom had low

serum TSH concentrations. Bone loss was measured in the distal forearm, femoral neck and lumbar spine. Premenopausal women, treated on average with 164 mcg L-T4/day for 8.5 years, had 2.67% less bone mass than controls (not statistically significant= NS), corresponding to an excess annual bone loss of 0.31% after 8.5 yrs. of treatment (NS). In contrast, postmenopausal women, treated on average with 171 mcg/day L-T4 for 9.9 yrs. had 9.02% less bone mass than controls, corresponding to a significant excess annual loss of 0.91% after 9.9 yrs. of treatment. Therefore, the meta-analysis did not find any statistically significant reduction in bone mass during prolonged L-T4 treatment in premenopausal women with reduced serum TSH. However, L-T4 treatment in postmenopausal women in doses leading to decreased serum TSH did result in significant excess annual bone loss compared to controls.

Pines et al (Gynecol Endocrinol 13(3):196-201, 1999) demonstrated L-thyroxine therapy prevented the beneficial effect of hormone-replacement therapy on bone mineral density in postmenopausal women.

(Note: excellent review articles on the adverse effects of levothyroxine on bone are by Haden et al in The Endocrinologist 6(4):322-327, 1996 and by Wolinsky-Friedland in Endocrin and Metabol Clinics of N.A. 24(2):395-421, 1995. Many of the above articles are summarized in these 2 articles. Woeber in Arch Int Med 2000; 160:1067-1071 refers to Greenspan's paper above and states that thyroid hormone excess may lead to a decrease in bone mineral density in postmenopausal women).

Leger et al (Acta Pediatr 86:704-10, 1997) demonstrated that long-term levothyroxine therapy had no detrimental effects on bone mineral density in children being treated for congenital hypothyroidism.

b. **Hypercalcemia**:

Thyroid hormones directly stimulate osteoclasts to enhance bone resorption. This leads to mild hypercalcemia, with concomitant suppression of serum PTH levels, modest elevations in bone alkaline phosphatase and negative calcium balance (Cooper, JAMA 259:3175, 1988).

c.**Bone Development**:

Premature craniosynostosis may occur in infants when they are overtreated with levothyroxine. Slipped capital femoral epiphysis has occurred in children during thyroxine treatment. Overtreatment with thyroid hormone may accelerate the bone maturation, limit catch-up growth and result in premature closure of the epiphyses and compromised adult height (Fisher: NEJM 318(10):632-34, 1988).

12.F. Overtreatment with levothyroxine may result in dysmenorrhea and infertility.

13. DRUG-DRUG INTERACTIONS:

13.A. Drugs that decrease TSH secretion:

Dopamine
Glucocorticoids
Octreotide

13.B. Drugs that alter thyroid hormone secretion:

Decrease secretion:
- Lithium
- Iodide
- Amiodarone
- Aminoglutethimide

Increase secretion:
- Iodide
- Amiodarone

13.C. Drugs that decrease T4 absorption:
- Colestipol
- Cholestyramine
- Colestipol/Niacin
- Aluminum hydroxide
- Ferrous sulfate
- Sucralfate

13.D. Drugs that alter T3 and T4 transport in serum:

Increased serum TBG concentration:
- Estrogens
- Tamoxifen
- Heroin
- Methadone
- Mitotane
- Fluorouracil

Decreased serum TBG concentration:
- Androgens
- Anabolic steroids (e.g. danazol)
- Nicotinic acid
- Glucocorticoids

Displacement from protein-binding sites:
- Furosemide
- Fenclofenac
- Mefenamic acid
- Salicylates

13.E. Drugs that alter T3 and T4 metabolism:

Increased hepatic metabolism:
- Phenobarbital
- Rifampin
- Phenytoin
- Carbamazepine

Decreased T4 5'-deiodinase activity:
- Propylthiouracil
- Amiodarone

Beta-adrenergic antagonist drugs
Glucocorticoids

13.F. Drugs whose efficacy is altered by thyroid hormone:

Digoxin:

The therapeutic effects of digitalis may be reduced by thyroid hormone. Serum digitalis levels may be decreased in hyperthyroidism or when a hypothyroid patient becomes euthyroid.

Anticoagulants:

T4 increases the response to anticoagulant therapy, therefore, a decrease in dose of anticoagulant therapy may be warranted with correction of the hypothyroid state or when the levothyroxine dose is increased.

Antidiabetic agents (insulin and sulfonylureas):

Thyroid hormone replacement therapy may increase insulin or other antidiabetic agent requirements.

13.G. Cytokines:

Therapy with interferon alpha is associated with the development of antimicrosomal antibodies in 20% of patients, and some have transient hyperthyroidism, hypothyroidism or both.

Therapy with interleukin-2 is associated with transient painless thyroiditis in about 20% of patients.

14. DRUG-DISEASE INTERACTIONS:

Disease states that affect levothyroxine requirements include:

a. Malabsorption (can increase dose requirements)

b. Disease states that alter serum TBG concentrations:

Increase TBG: pregnancy, infectious hepatitis and acute intermittent porphyria;

Decrease TBG: nephrosis, acromegaly, severe hypoproteinemia, severe liver disease (TBG may be decreased or normal).

c. Concomitant cardiovascular disease:

Decrease the levothyroxine replacement dose to avoid precipitation of angina, arrhythmias, MI and CHF.

d. Concomitant diabetes mellitus:

An increase in the dose of insulin or other antidiabetic agents may be necessary. Diabetic control should be carefully monitored, especially when thyroid therapy is started, changed or discontinued.

e. Concomitant adrenocortical insufficiency:

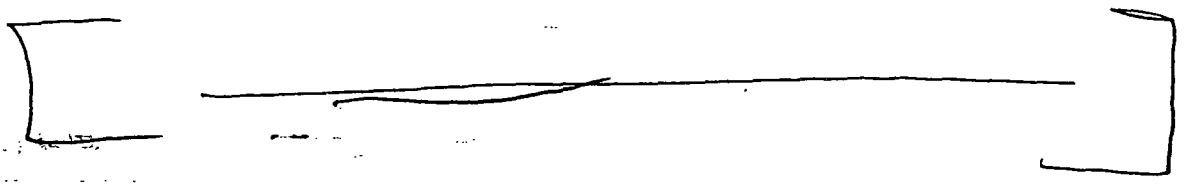
Thyroid hormone replacement therapy should not begin until glucocorticoid replacement therapy has started, since acceleration of the metabolic clearance of glucocorticoid by thyroid hormone may precipitate an acute adrenal crisis if ACTH secretion is compromised.

15. OVERDOSE:

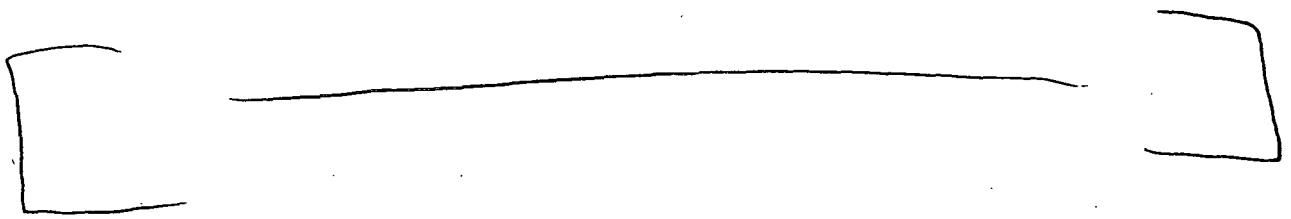
Accidental or intentional acute or chronic overdose includes the signs and symptoms of thyrotoxicosis: palpitations, tachycardia, arrhythmias, increased blood pressure, chest pain, angina, shortness of breath, CHF, heat intolerance, increased sweating, fever, weight loss, vomiting, diarrhea, muscle weakness, periodic paralysis, tremors, hyperactivity, nervousness, irritability, anxiety, agitation, confusion, disorientation. Cerebral embolism, coma and death have been reported. Grand mal seizures were reported in a 30 month old boy who ingested 18 mg L-T4 (Kulig et al JAMA 1985, 254:2109). Some patients have developed tolerance to the drug. The majority of the preparations ingested were either dessicated thyroid or levothyroxine. However, Hedberg (NEJM 316:993, 1987) reported palpitations, fatigue and tremor in individuals ingesting ground beef contaminated with thyroid.

16. **Levothyroxine Labeling Template:**

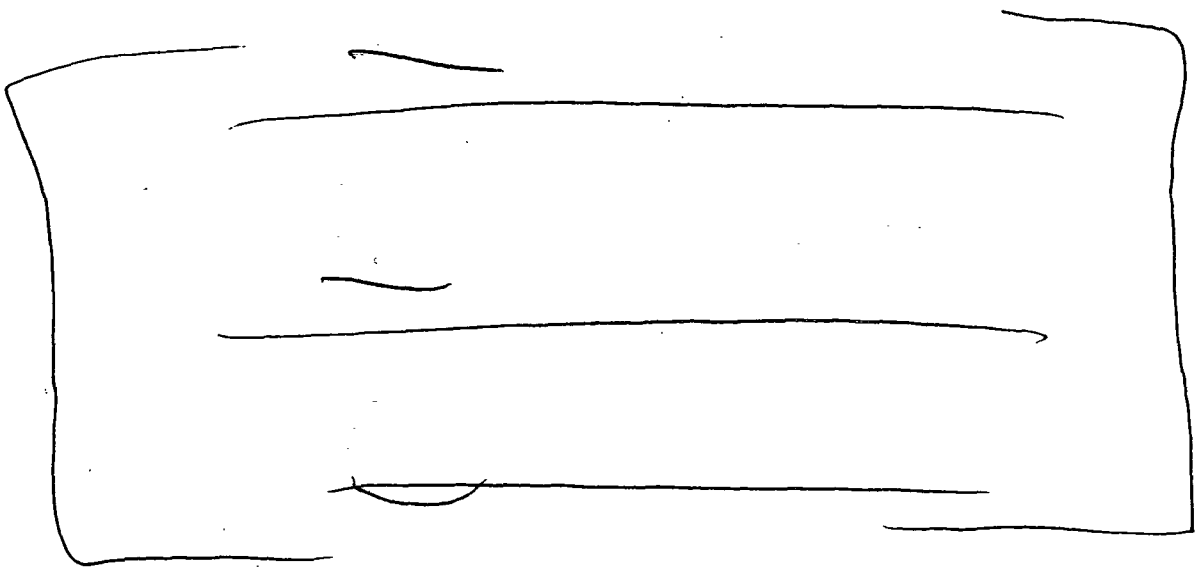
It is recommended that the following changes be made to the March 20, 2001 FDA levothyroxine labeling template:



2. **WARNINGS:**



3. **PRECAUTIONS:**



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Draft Labeling
(not releasable

STORAGE CONDITIONS
[Product-specific information supplied by applicant]

Rx ONLY

MANUFACTURER
[Product-specific information supplied by applicant]

17. Evaluation and Regulatory Action:

Levothyroxine sodium tablets are safe and effective for the indications stated in the draft labeling for this product. However, it is important to bear in mind that levothyroxine sodium is a drug with a narrow therapeutic index and there may be serious adverse consequences if the dose is not specifically titrated to the needs of the individual patient. Specifically, undertreatment of an infant with congenital hypothyroidism may have adverse consequences on intellectual development and growth. Undertreatment of a child with acquired hypothyroidism may adversely affect school performance, as well as growth and pubertal development. Undertreatment of hypothyroidism in an adult may adversely affect mentation (slowness of thought and memory loss), myocardial performance (impaired myocardial contractility) and lipid levels. Inadequate suppression of TSH by levothyroxine in a patient with well-differentiated thyroid cancer, may stimulate tumor growth and growth of metastases. Conversely, overtreatment is to be avoided. Overtreatment of congenital hypothyroidism with levothyroxine sodium may disrupt the tempo of brain maturation and may result in premature craniosynostosis. Excess T4 replacement in children may accelerate the bone age leading to premature closure of the epiphyses and compromised final adult height. In the adult, overtreatment may have adverse consequences on the myocardium and bone. Therefore, it is critical to precisely titrate the dose of levothyroxine sodium to achieve and maintain the euthyroid state clinically and biochemically, thus avoiding the adverse consequences of under- and overtreatment, unless TSH suppression is the objective as in patients with well-differentiated thyroid cancer. To achieve this goal, it is essential to have levothyroxine drug products that demonstrate consistent potency and stability.

In addition, a 25 mcg dosage strength that meets chemistry and biopharm criteria for approval, is essential for proper labeling of the product for safe and effective use given that in certain clinical situations, levothyroxine sodium dosing is initiated at 12.5-25 mcg/day and increased in 12.5-25 mcg dosing increments.

From a clinical standpoint, an approval letter may be issued to Genpharm for their levothyroxine sodium tablets provided they submit draft labeling which conforms to FDA's proposed labeling template for this class of products.

/S/
Jean Temeck, M.D.

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Note: A draft algorithm for pediatric formulations is appended. This draft was written by the Pediatric Formulations Working Group and was disseminated at the July, 13, 2000 Pedicomm meeting.

/S/

Jean Temeck, M.D.

cc. NDA Arch 21,292
NDA Division file
HFD-510: Dr. Ahn, Dr. Johnson, Dr. Davis-Bruno and Mr. McCort

/s/

Jean Temeck
4/4/01 01:56:16 PM
MEDICAL OFFICER

David Orloff
4/6/01 04:26:43 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

NDA: 21,292
Drug: [redacted] (levothyroxine sodium tablets)
Sponsor: Genpharm
Date: 3/30/01

MEMO TO FILE

The sponsor submitted a Financial Disclosure statement regarding the above NDA and certified that they did not enter into any financial arrangement with [redacted], the Medical Director and Principal Investigator for the bioavailability studies conducted under this NDA.

Jean Temeck, M.D.

/s/

Jean Temeck
3/30/01 07:39:28 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Safety Summary not needed.