CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-342

MEDICAL REVIEW(S)

NDA # 21-342
Levo-T (levothyroxine sodium tablets)
Mova Pharm Corp.
Dosage Strengths: 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg
Date submitted: May 1, 2001 (CDER Stamp Date)
Date of review: February 15, 2002

Medical Team Leader review of NDA[1]

Administrative background

In the Federal Register 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 has recently been extended to August 14, 2001.

Manufacturers wishing to continue to market oral T4 products after August 14, 2001 are expected to submit NDAs, including 505(b)(2) applications, that contain literature references supporting the safety and effectiveness of LT4 for the proposed indications. In addition, bioavailability and *in vitro* dissolution studies are required. In short, this approach to development of levothyroxine-containing new drug products relies on the fact that levothyroxine itself is a safe and effective treatment for supplementation or replacement in patients with insufficient endogenous thyroid hormone and for suppression to TSH in patients with thyroid nodules or cancer. Therefore, the approvability of an oral T4 product depends upon demonstration of acceptable quality, quantity, and performance as assessed by manufacturing information, data from stability studies, and the results of bioequivalence/bioavailability and dissolution studies.

The Levo-T NDA was submitted with the clinical section in accordance with the August 1997 FR notice, with the required section addressing chemistry, manufacturing, and stability, and with additional content in accordance with Division guidance on the bioavailability/bioequivalence and dissolution studies required for approval of levothyroxine-containing products.

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

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 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 class labeling for LT4 drug products that is appended to Dr. Temeck's review. With this submission, Dr. Temeck has made recommendations to include the effects of LT4 on bone mineral density under the PRECAUTIONS section and other minor changes to the levothyroxine labeling template (see section XI of Dr. Temeck's review). These recommendations will also be made to all currently approved LT4 drug products.

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 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 or 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

Reduced stability testing of lots involving the 25, 50, 100, and 300 mcg doses revealed satisfactory 18-month stability for all strengths at 25°C and 60% RH. Stability studies at accelerated storage conditions (40°C, 75% RH) were not conducted with FDA concurrence

Although the 25 mcg tablets exhibited the highest observed stability overage, a different analytical method showed a lower release value within the acceptable range to allow the drug products to release at 100% of label claim. On the basis of these results,

the recommendation of ONDC is for approval with an 18-month expiry for all 11 tablet strengths.

A Phase 4 commitment for an in-process specification for the levothyroxine sodium assay for the [redacted] stage was recommended within one year of approval. The sponsor has agreed to providing the Agency with this information.

Clinical Pharmacology and Biopharmaceutics
Dr. Steven Johnson reviewed the results of a relative bioavailability (BA) study, a dosage-form proportionality study, and one *in vitro* dissolution study. The study designs and protocols are described in detail in Dr. Johnson's review. The results for the BA study demonstrated that Levo-T tablets (600 mcg administered as two 300 mcg tablets) are 99% bioavailable relative to an oral solution of T4 (600 mcg of Synthroid ™ prepared from three 200 mcg vials of the injectable formulation). The dosage-form proportionality study established that the 50 ug, 100 ug, and 300 ug tablets are dosage-form equivalent. On the basis of this finding, the requirement for demonstration of dosage-strength proportionality for the other tablet strengths is waived.

The results of the *in vitro* dissolution study on 3 lots each of the 11 to-be-marketed strengths demonstrated rapid dissolution but considerable intra- and inter-lot variability. Additional data were requested of the sponsor including single point dissolution data of each of the to-be-marketed strengths at the 15 minute time point. Due to the rapid dissolution, a single-strength study using non-sodium lauryl sulfate (SLS) media was also requested. Review of these additional data still revealed an error in the dissolution technique; however, Dr. Johnson and OCPB concluded that sufficient data have been submitted to justify setting a dissolution tolerance specification. In addition, the dissolution method should include an SLS-containing media.

Data Integrity
The Division of Scientific Investigations conducted an audit of the analytical portions of the two biovailability/bioequivalence studies. There were no problems with the analytical section; however, there was a drug accountability issue where the CRO did not randomly obtain drugs from the 90- and 1000-count bottles of the to-be-tested dosage strengths as per protocol. Testing was conducted only on drug from the 90-count bottles. Dr. Johnson did not consider this a significant problem preventing the approval of this product.

Summary and conclusions
Levothyroxine is a safe and effective option 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 or 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.

Recommendation
This NDA may be approved. The proposed product name, Levo-T, is acceptable.

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

Recommendation code: *AP*

Concur: Dr. Parks
/S/
2-22-99

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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
2/25/02 04:16:54 PM
MEDICAL OFFICER

David Orloff
2/28/02 06:08:39 PM
MEDICAL OFFICER
Concur with Dr. Parks. Recommend approval.

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	21-342	**Application Type:**	NDA
Sponsor:	Mova Pharm Corp.	**Proprietary Name:**	Levo-T
Investigator:		**USAN / Established Name:**	Levothyroxine sodium
Category:	Thyroid hormone replacement	**Route of Administration:**	Oral
Medical Reviewer:	Jean Temeck, M.D.	**Review Date:**	1/18/02

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
April 30, 2001	May 1, 2001	NDA	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
October 19, 1999	NDA 21-210	Unithroid: Jerome Stevens Pharm.
July 28, 2000	NDA 21-301	Levoxyl: Jones Pharma, Inc.

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.

The sponsor has fulfilled the clinical requirements of the NDA as specified in the Notice by referencing representative articles from the published literature on this issue. This review summarizes in detail the 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.

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

OUTSTANDING ISSUES: Submit to the sponsor a copy of FDA's levothyroxine sodium labeling template.

RECOMMENDED REGULATORY ACTION:

New Clinical Studies:	_____ Clinical Hold	_____ Study May Proceed
NDA, Efficacy/ Label Supplement:	X Approvable	_____ Not Approvable

SIGNATURES: Medical Reviewer: Jean Temeck, M.D. Date: 1/18/02

Medical Team Leader: _____ Date: _____

Executive 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.

The drug product itself, levothyroxine sodium, 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 the potency of the product. Hennessey (ref. 127) reported that the downward trend in levothyroxine replacement dose paralleled modifications in formulation with resultant increases in product potency and bioavailability.

The variability in stability and potency from batch-to-batch for a given levothyroxine sodium drug product and across those made by various manufacturers of this drug, has resulted in numerous recalls due to the release of subpotent or superpotent tablets with their attendant adverse clinical consequences.

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, ref. 127) 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 sponsor has fulfilled the clinical requirements of the NDA as specified in The Notice by submitting a review of the published literature pertaining to the safety and efficacy of levothyroxine sodium products. This review summarizes in detail published literature relating to the safety and efficacy of levothyroxine sodium in both adult and pediatric patients, as replacement or supplemental therapy of hypothyroidism and to suppress TSH in the treatment of goiter, nodules and thyroid cancer. Based on this review, levothyroxine sodium drug products are safe and effective for the stated above indications, provided they demonstrate consistent potency and stability and are used as directed. A levothyroxine labeling template has also been prepared by the Agency and is attached.

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

A waiver regarding conduct of clinical trials in pediatric patients may be granted because the published literature adequately supports the safe and effective use of levothyroxine sodium drug products for the indications specified in FDA's levothyroxine labeling template.

Recommended Regulatory Action:

Approval from a clinical perspective provided the sponsor submits draft labeling which conforms to FDA's levothyroxine sodium labeling template.

APPEARS THIS WAY
ON ORIGINAL

Table of Contents:

I. INTRODUCTION AND BACKGROUND:

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. To avoid the adverse clinical consequences of either over- or undertreatment, a levothyroxine sodium product must demonstrate consistent potency and stability over the shelf life of the product.

This NDA was submitted by Mova Pharm. Corp. in response to FDA's August 14, 1997 Federal Register Notice. As required by The Notice, the sponsor has submitted the results of 2 bioavailability studies. One of these studies was to establish bioequivalence between two 300mcg 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. The sponsor has also included, as required by The Notice, representative examples from the published literature pertaining to the efficacy and safety of oral levothyroxine sodium products, to fulfill the clinical requirements of the NDA.

Dosage form and route of administration: tablets for oral administration.

Domestic and foreign marketing history: Levo-T has not yet been marketed by the Mova Pharm. Corp. because this is a new formulation.

II. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY OR BIOPHARMACEUTICS REVIEWS:

See the reviews prepared by Dr. Lewis, chemist; Dr. Davis-Bruno, pharm/tox and Dr. Johnson, biopharmaceutics.

III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS:

See Dr. Johnson's biopharmaceutics review of the bioavailability studies conducted by the sponsor. The clinical review will discuss only the safety results of these studies and these results may be found in section VII: Review of safety.

Clinical Pharmacology of Thyroid Hormones:

a. 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.

b. Effects of thyroid hormones on metabolism, growth and development, maturation and target tissues:

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.

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.

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.

Effects of thyroid hormones on maturation:
Thyroid hormones are required for normal maturation of bone and the central nervous system (CNS).
Mental retardation may result from 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.

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.

Pharmacokinetics:

a. 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.

b. Absorption, distribution, volume of distribution, metabolism and elimination:
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.

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.
Although thyroid hormones do not readily cross the placenta (Fisher, ref. 95), they do to a certain extent as demonstrated by Vulsma et al (ref. 294). They estimated that the maternal-to-fetal ratio of serum T_4 was roughly 3:1.
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.

Volume of distribution:
In Oppenheimer's study (ref. 208), 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.

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.

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.

Drug-Drug Interactions: (e.g. Surks et al, ref. 269)

Drugs that decrease TSH secretion:	Dopamine, Glucocorticoids and Octreotide
Drugs that alter thyroid hormone secretion: Decrease secretion: Increase secretion:	 Lithium, Iodide, Amiodarone and Aminoglutethimide; Iodide and Amiodarone
Drugs that decrease T4 absorption:	Colestipol, Cholestyramine, Colestipol/Niacin, Aluminum hydroxide, Ferrous sulfate and Sucralfate
Drugs that alter T3 and T4 transport in serum: Increased serum TBG concentration: Decreased serum TBG concentration: Displacement from protein-binding sites:	 Estrogens, Tamoxifen, Heroin, Methadone, Mitotane and Fluorouracil; Androgens, Anabolic steroids (e.g. danazol), Nicotinic acid and Glucocorticoids; Furosemide, Fenclofenac, Mefenamic acid and Salicylates
Drugs that alter T3 and T4 metabolism: Increased hepatic metabolism: Decreased T4 5'-deiodinase activity:	 Phenobarbital, Rifampin, Phenytoin and Carbamazepine; Propylthiouracil, Amiodarone, Beta-adrenergic antagonist drugs and Glucocorticoids
Drugs whose efficacy is altered by thyroid hormone: Digoxin: Anticoagulants: Antidiabetic agents (insulin and sulfonylureas):	 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. 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. Thyroid hormone replacement therapy may increase insulin or other antidiabetic agent requirements.
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 pts.

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.

IV. DESCRIPTION OF CLINICAL DATA AND SOURCES:

As stated in the August 14, 1997 FRN, representative articles from the published literature will support the safety and efficacy of levothyroxine sodium in both adult and pediatric patients, as replacement or supplemental therapy of hypothyroidism and to suppress TSH in the treatment of goiter, nodules and thyroid cancer. This review is a summary of representative articles from the published literature.

The following is a summary of pertinent clinical background information related to the clinical presentation of hypothyroidism, laboratory evaluation and the signs and symptoms of overdosage with levothyroxine sodium drug products.

The signs and symptoms of hypothyroidism may include, by body system, the following:

Body System	**Hypothyroidism Signs and Symptoms**
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

The signs and symptoms of overtreatment with levothroxine sodium are those of hyperthyroidism:

Body System	Overtreatment with levothroxine: Signs and Symptoms
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

Note: Billewicz et al (ref. 29) developed a statistical approach to quantifying clinical signs of hyper and hypothyroidism in a way that they can be distinguished from a euthyroid state.

The signs and symptoms of **accidental or intentional acute or chronic overdosage** include 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, ref. 150). Some patients have developed tolerance to the drug. The majority of the preparations ingested were either dessicated thyroid or levothyroxine. However, Hedberg (ref. 124) reported palpitations, fatigue and tremor in individuals ingesting ground beef contaminated with thyroid.

The general management of thyroid storm encompases symptomatic and supportive care. Supportive care entails administration of intravenous fluids to treat dehydration and shock, respiratory support, control of hyperpyrexia and hypoglycemia. Emesis or gastric lavage, activated charcoal and cholestyramine may be used to decrease absorption. Digitalization may be needed to treat congestive heart failure or control ventricular rate in patients with atrial fibrillation. β-receptor antagonists, e.g. propranolol, may be administered to control increased sympathetic activity. To inhibit thyroid hormone synthesis, large doses of antithyroid agents, such as Tapazole or PTU, may be given po or NG or by rectum. PTU may be preferable because it also inhibits the peripheral conversion of T_4 to T_3. This should be followed in 1-2 hours by large doses of iodine by mouth or IV to inhibit thyroid hormone release. Glucocorticoids may be given to provide adrenal support and inhibit the peripheral conversion of T_4 to T_3 (refs.45, 49, 65, 133, 279, 297 and 309).

Plasmapheresis and/or charcoal hemoperfusion have been used successfully in conjunction with other treatment modalities (such as propanolol and hydrocortisone) to treat acute levothyroxine overdose in adults (Binimelis, ref. 30). However, experience with these treatment modalities for this indication is very limited and conclusive studies are lacking (Binimelis, ref. 30). Charcoal hemoperfusion was ineffective for this purpose in a child who accidentally ingested 12 mg of levothyroxine (Lehrner, ref. 159). Gerard (ref. 105) report successful treatment of acute levothyroxine overdose in a 3 year old girl who received exchange transfusion in conjunction with gastric lavage, barbiturates and antipyretics. These aggressive measures are generally reserved for patients who manifest continued clinical deterioration despite conventional treatment (Burman, ref. 49; Burch, ref. 45; Zimmerman, ref. 309 and Cooper, ref. 65).
Treatment of the 30 month old boy who ingested 18 mg L-T4 consisted of emesis, gastric lavage, activated charcoal, oral magnesium sulfate, phenobarbital and propranolol (Kulig, ref. 150).
In general, it appears that children tolerate acute ingestion of levothyroxine much better than adults (Gerard, ref. 105; Kulig, ref. 150 and Lin, ref. 162). Therefore, aggressive therapeutic attempts in asymptomatic patients are not justified (Lin, ref. 162). After evacuation of the stomach by emesis or gastric lavage, activated charcoal may be administered to decrease absorption and propranolol administered to treat adrenergic overactivity. (Lin, ref. 162).

The **laboratory evaluation of hypothyroidism** includes the following:
The 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.

V. CLINICAL REVIEW METHODS:

The published literature submitted by the sponsor was reviewed as well as the safety data from the 2 bioavailability studies conducted by the sponsor.
The sponsor stated in their Financial Disclosure statement they they did not enter into any financial arrangement with [redacted] who conducted the bioavailability studies.

VI. REVIEW OF EFFICACY:

Historical Overview:

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, .

Review of Efficacy:

a. Hypothyroidism (including Hashimoto's disease) and Subclinical Hypothyroidism:

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 (ref. 64) and Monzani (ref. 188) 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. Arem and Patsch (ref. 11) demonstrated normalization of serum TSH in patients with subclinical hypothyroidism who received an appropriate dose of levothyroxine. Achievement of a euthyroid state in these patients was accompanied by a statistically significant decrease in plasma LDL-c and apolipoprotein B levels compared to baseline. However, Roti (ref. 239) mentions that the treatment of subclinical hypothyroidism with levothroxine is not recommended by all because it is not clear if it consistently progresses to overt hypothyroidism, although those with antithyroid antibodies often do, and the beneficial effects of thyroid hormone treatment of this condition remain somewhat controversial (e.g. the variability in the reported lipid responses to levothyroxine therapy). Roti does state, however, that he and the other authors of this article generally treat patients with this disorder.

The efficacy of levothyroxine sodium in the treatment of Hashimoto's thyroidits was demonstrated by Hegedus (ref. 125). 13 hypothyroid women with goitrous Hashimoto's thyroidits received levothyroxine therapy for 24 months to render them euthyroid. After 24 months of treatment, thyroid volume significantly decreased from baseline (mean change: -32%) and this change occurred in conjunction with normalization or near normalization of thyroid function (all patients became euthyroid with normal free T_4 and T_3 index levels, but 4 patients still had an elevated serum TSH). 6 of the 13 patients no longer had a clinically detectable goiter.

b. Nontoxic Goiter and Thyroid Nodules:

Roti (ref. 239) reviewed the efficacy of levothyroxine therapy in the treatment of euthyroid diffuse goiter. He refers to several articles that reported a decrease in thyroid volume after 12 months of L-T_4 therapy. However, he does state that there is no

consensus regarding treatment of these patients, a statement which is echoed by Toft (ref. 275). He provides the following guidelines for management of these patients: measurement of TSH at baseline using a sensitive assay to be certain it is not already suppressed, administration of T_4 suppression therapy to patients <40 years old and interruption of treatment for failure to reduce goiter volume after 6 months. He does not recommend treatment of patients >60 years since the results of such treatment have not been proven and the risks of overtreatment in this age group are potentially more serious.
The efficacy of levothyroxine as suppressive therapy in the treatment of nontoxic nodular goiter was demonstrated by Miccoli (ref. 185). 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).
A placebo-controlled trial conducted by Berghout (ref. 25) demonstrated the efficacy of L-T_4 suppressive therapy in patients with sporadic non-toxic goiter (either diffuse or nodular). After 9 months of L-T_4 therapy administered at a mean dose of 2.5 mcg/kg/day, 58% of patients decreased their thyroid volume as measured by ultrasonography compared to 5% in the placebo group. The mean decrease in thyroid volume in the responders was 25%. After discontinuation of treatment, thyroid volume increased in the responders and returned to baseline values after 9 months of follow-up.
The efficacy of levothyroxine in arresting the growth or in reducing the volume of benign solitary thyroid nodules was demonstrated by LaRosa (ref. 153). However, others (Gharib, ref. 107 and Reverter, ref. 227) demonstrated no benefit. Roti points out that the variability in reported responses to T_4 suppressive therapy may be related to whether the nodule was autonomous or not given that T_4 suppressive therapy is unlikely to decrease the size of an autonomous nodule. Roti presents a protocol developed by Ridgway to determine this.
A number of articles in the literature (referenced below in parenthesis), point out that the value of levothyroxine suppressive therapy in the treatment of benign (nontoxic) nodular disease (soliary nodules and multinodular goiter) is controversial and the degree to which TSH should be suppressed in these conditions, is uncertain. (Hermus and Huysmans, ref. 128; Roti, ref. 239; Mandel, ref. 172; Singer, ref. 257; and Toft, ref. 275). However, the target levels for TSH suppression in these conditions are generally higher than those recommended for thyroid cancer. Burch (ref. 46) and Mandel (ref. 172) recommend that TSH be suppressed to 0.5-1.0 mU/L in patients with non-toxic multinodular goiter. Burch (ref. 46) and Gharib (ref. 108) recommend that TSH be suppressed to 0.1 or 0.2 - 0.5 mU/L in patients with solitary non-toxic benign nodules.
Before initiating thyroid hormone suppressive therapy in a patient with nontoxic diffuse goiter or nodular thyroid disease, it is imperative that a serum TSH level be obtained using a sensitive assay to determine if the TSH is already suppressed. These patients may have autonomous thyroid hormone production and subclinical hyperthyroidism and giving them thyroxine therapy may precipitate overt thyrotoxicosis. In addition, no shrinkage of the goiter or nodule would be expected to occur if the serum TSH is already suppressed (Cooper, ref. 63; Roti, ref. 239; Hermus and Huysmans, ref. 128; Mandel, ref. 172; Singer, ref. 257; Toft, ref. 275 and Farewell and Braverman, ref. 87). Roti and Singer both mention the value of also performing an ^{123}I scan in such circumstances. They also both mention that they generally do not treat elderly patients with multinodular

goiter with levothyroxine suppressive therapy due to the risk of precipitating thyrotoxicosis from areas of autonomy which are likely to be present in the goiter. Farewell and Braverman state that suppression therapy for nodular thyroid disease should be generally avoided in older patients and in those with coronary artery disease.

c. Thyroid Cancer:

T4 as an adjunct to surgery and ^{131}I therapy is effective because tumor recurrence rates are higher if T4 is not given after surgery (Mazzaferri, ref. 177). Although the degree of TSH suppression which is optimal to inhibit potential tumor growth in patients with well differentiated thyroid cancer is not known, it is general practice to suppress the TSH to < 0.1 mU/L (Mandel, ref. 172 and Ain, ref. 4). Mazzaferri (ref. 177) that for most patients with thyroid cancer, the dose of T4 to be used should suppress TSH to just below the lower limit of the normal range of the assay being used. However, the level of TSH suppression to target may vary with tumor risk (low versus high). Mazzaferri (ref. 177) states that some clinicians suppress TSH to 0.05-0.1 uU/ml in low-risk patients and to <0.01 uU/ml in high-risk patients and a few clinicians advocate the latter target in all patients. Singer (ref. 257) and Hershman and Gordon (ref. 130) recommend that TSH be suppressed below 0.01 mU/L in patients with high risk tumors. Toft (ref. 275) provides a general recommendation of TSH suppression to <0.01 mU/L in patients with well differentiated thyroid cancer. In addition, Singer (ref. 257) mentions that the duration of suppression has not been established.

d. Maternal Hypothyroidism:

The importance of treating maternal hypothyroidism during pregnancy, even if mild, was highlighted by Haddow (ref. 115). Neuropsychological testing of the 7 to 9 year old offspring (none of whom had hypothyroidism as newborns) of 62 women with high serum TSH levels during pregnancy was compared to that in the offspring of 124 matched women with normal serum TSH levels. Full-scale IQ scores in the offspring of the women with high serum TSH levels was, on average, 4 points lower compared to children of the control group; 15% had scores of 85 or less compared to 5% of the matched control children. Of the 62 women with thyroid deficiency, 48 were not treated for the condition during pregnancy. The full-scale IQ scores of their children averaged 7 points lower than the control children; 19% had scores of 85 or less. In conclusion, this study demonstrated that hypothyroidism in pregnant women can adversely effect the child's neuropsychological development even when the pregant woman's hypothyroidism is mild.

Pop (ref. 219) reported that children of women with free T_4 levels below the 5^{th} and 10^{th} percentiles at 12 weeks gestation had significantly lower scores (by 14 and 7 points, respectively) on the Bayley Psychomotor Developmental Index scale at 10 months of age compared to children of mothers with higher free T_4 values. He concludes that a maternal free T_4 concentration in the low normal range (below the 10^{th} percentile) at 12 weeks gestation may be an important risk factor for impaired psychomotor development.

Indications and Use:

Based on published literature (representative articles being: Roti, ref. 239; Toft, ref. 275; and Farewell and Braverman, ref. 87), levothyroxine sodium is indicated for the following conditions:

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 (ref. 276) 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.

VII. REVIEW OF SAFETY:

a. Review of Safety in the Bioavailability Studies:

Study No. 990673:

This bioavailability study was an open-label, single-dose, randomized, 2-way crossover comparing 600 ug Levo-T (dose: 2 tablets x 300 ug/tablet= 600 ug) to a Levothyroxine oral solution (prepared from Levothyroxine Sodium for Injection) in 28 normal healthy volunteers (14 males and 14 females). A total of 57 adverse events were reported, three of which were judged unrelated to study drug. Four subjects did not complete crossover due to adverse events. One of these subjects had received only the Levo-T tablets and had experienced headache, nausea and dizziness before dosing and vomiting afterwards. The adverse events experienced by the 3 subjects who received only the oral solution included headache, dizziness, nausea, vomiting, abdominal cramps, coldness, shivering, feeling tired, feverish, sore eyes and leg pain. For the Levo-T tablets, 7 subjects reported 15 adverse events considered possibly, probably or remotely drug-related. 3 events of headache were reported and 1 event of each of the following: nausea, vomiting, feeling hot/feeling feverish, feeling hot/cold, feeling cold, head feeling heavy, weak feeling in legs, pain in legs, pulling sensation in the leg, genital area odor, genital area itching and genital area burning sensation. On the oral solution, 13 subjects reported 39 drug-related adverse events. The most common adverse events were: headache (7 events), nausea (7

events) and feeling cold (3 events). There were 2 events for each of the following: abdominal cramps/pain, shivering and numb hand/cold hand. There was 1 event of each of the following: dizziness, vomiting, feeling hot/feverish, intermittent hot flashes, eyes feeling heavy, sore eyes, feeling tired, numb tongue, pain in neck, pain in legs, weak feeling in legs, back pain, loss of hair, runny nose, earaches and sinus infection. No adverse events associated with vital signs were reported.

Study No. 990675:
This was an open label, single-dose, randomized, 3-way crossover study to compare the dosage-form equivalence among the 50 mcg, 100 mcg and 300 mcg dosage strengths of Levothroid under fasting conditions in 30 normal volunteers (15 males and 15 females). Each dosage strength was administered in crossover fashion, with a 35-day wash-out period, and in multiples to provide a single 600 mcg dose (12 x 50 mcg tablets, 6 x 100 mcg tablets, 2 x 300 mcg). One subject was withdrawn from the study after experiencing the following adverse events after ingestion of six 100 ug tablets: dizziness, blurred vision, head numbness, feeling cold, headache, abdominal pain/cramping and lower back pain. A total of 36 events were reported by 12 subjects, including 7 events judged unrelated to the study drug. Of the drug-related adverse events, headache was the most common (11 reports) followed by abdominal pain/cramps/burning (3 events) and dizziness and rash on shoulder/itchy (2 events each). There was 1 event of each of the following: numbness of the head, blurred vision, feels cold, lower back pain, insomnia, diaphoresis/sweating, ears ringing, herpes simplex on mouth, red spot on arm, sleepinesss and small bump on check. Laboratory and vital signs were unremarkable.

b. Review of Safety Based on the Published Literature Pertaining to:
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.

Potential Adverse CNS Effects From Under-or Overtreatment:
See section VIII. of this review. In addition, pseudotumor cerebri has been reported in children receiving levothyroxine therapy.

End-organ effects:
There is a concern (Toft, ref. 276) that doses of thyroxine which suppress TSH secretion may be associated with end organ effects, such as changes in nocturnal heart rate, systolic time interval, urinary sodium excretion and liver and muscle enzyme activities. The potential adverse effect of suppressive doses of levothyroxine on bone, namely decreased bone density and accelerated demineralization in pre- and post-menopausal women are also mentioned.
Ross (ref. 235) mentions the possible abnormalitiies that have been reported in patients with subclinical hyperthyroidism: increased heart rate, reduced day-to-night ratio of urinary sodium excretion and urine flow, shortened systolic time intervals, decreased bone mineral density and elevations of the liver enzymes glutathione S-transferase,

alanine aminotransferase and γ-glutamyltransferase. Decreased serum creatine kinase activity and increased sex hormone-binding globulin have also been reported. The author recommends that the new sensitive TSH assay be used to monitor patients taking levothyroxine to prevent potential adverse consequences of overzealous treatment with this drug. Patients taking levothyroxine for replacement therapy should have normal serum sensitive TSH concentrations. Patients taking suppressive doses should take the lowest possible dose to achieve the desired clinical and biochemical effect. For patients with thyroid cacner, the serum sensitive TSH concentration should be suppressed to undetectable levels. For patients with goiter or thyroid nodules, suppression of TSH to subnormal values may be sufficient.
Hyperthyroidism may be associated with abnormalities in hepatic function including mild increases in serum alanine and aspartate aminotransferase, alkaline phosphatase and bilirubin; occasionally jaundice is clinically evident. Liver histology is normal or shows mild hepatocellular injury (Utiger, ref. 279).

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 (ref. 146).
a. **Undertreatment**:
The heart may be affected by changes in serum thyroxine within the "normal" range in mildly hypothyroid patients as demonstrated by Ridgway (ref. 228). 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, ref. 195). Also reported here was that hypercholesterolemia may be exaggerated in hypothyroid patients.

b. **Overtreatment**:
Sawin (ref. 249) 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 (ref. 247) 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 (ref. 100) reported that as many as 13% of patients with unexplained atrial fibrillation had biochemical evidence of hyperthyroidism.
Leese (ref. 157) 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 (ref. 32) 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 (ref. 31) again reported increased LV mass index in patients on levothyroxine suppressive therapy. This was associated with significantly enhanced systolic function.

Grund (ref. 113) 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 (ref. 88) 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, ref. 36, reported that LV diastolic dysfunction may be a cause of CHF; Cuocolo, ref. 66, reported LV hypertrophy in association with impaired diastolic filling).

Jennings (ref. 138) 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 (ref. 218) reported that levothyroxine replacement therapy is associated with an increase in basal, average and maximal heart rates.

Ching (ref. 59) 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 (ref. 183) 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, ref. 247). Others (Proskey, ref. 222; Amikan and Riss, ref. 10; Kotler, ref. 148; Cheah, ref. 58; Martinez-Rovira, ref. 175; Douglas, ref. 78; Barnett, ref. 16; Resnekov, ref. 226 and Wei, ref. 300), 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, ref. 101).
(Note: an excellent review article on the adverse effects of levothyroxine on the heart is by Haden, ref. 116. Many of the above articles are summarized in this article. Woeber, ref. 306 refers to Ching's paper above and states that thyroid hormone excess may have adverse cardiac consequences).

Long-term Adverse Effects on Bone:

a. On Bone Mineral Density:

Franklyn (ref. 102) 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 ± S.D. thyroxine dose was 191 ± 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 (ref. 280) 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 (ref. 236) found a 9% decrement in forearm cortical bone density in 12/28 premenopausal patients who had been receiving levothyroxine therapy for ≥ 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 (ref. 211) 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 (ref. 74) reported that suppressive doses of T4 significantly reduce bone mineral measurements (femoral neck) in both pre- and postmenopausal women with thyroid carcinoma. Also, bone turnover as assessed by serum G1a-protein was increased in all patients.
Kung (ref. 151) reported that 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. 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 (ref. 263) 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 (ref. 110) 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 (ref. 2) 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.

Jodar (ref. 139) reported a small reduction in BMD at the distal third radius in pre- and post-menopausal women on chronic suppressive levothyroxine therapy for thyroid cancer. In a subset of patients followed for at least 18 additional months, there was a significant although mild reduction in femoral neck BMD, without differences between pre- and postmenopausal women, and which correlated with prior serum T_3 and intact PTH levels.

Faber (ref. 86) 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 (ref. 216) demonstrated L-thyroxine therapy prevented the beneficial effect of hormone-replacement therapy on bone mineral density in postmenopausal women.

Schneider (ref. 251) compared BMD in 196 post-menopausal women taking thyroid hormone for a mean duration of 20.4 years to BMD in 795 women not using thyroid hormone. Women taking daily thyroxine-equivalent doses $\geq$ 200 mcg had significantly lower midshaft radius and hip BMD compared to those taking <200 mcg. Daily doses $\geq$ 1.6 mcg/kg were associated with lower bone mass at the ultradistal and midshaft radius, hip and lumbar spine compared with nonuse, whereas doses < 1.6 mcg/kg/day were not associated with lower BMDs. Women taking both estrogen and thyroid hormone at doses $\geq$ 1.6 mcg/kg/day had significantly higher BMDs at all 4 sites (specified above) compared to those taking the same thyroid hormone dose alone. BMDs in women taking

both estrogen and thyroid hormone were comparable to BMDs in women taking only estrogen. Therefore, in this study, estrogen prevented thyroid hormone-associated loss of bone density in postmenopausal women.
Roti (ref. 239) 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.
Leger (ref. 158) and Kooh (ref. 147) demonstrated that long-term levothyroxine therapy had no detrimental effects on bone mineral density in children being treated for congenital hypothyroidism.
(Note: excellent review articles on the adverse effects of levothyroxine on bone are by Haden, ref. 116 and by Wolinsky-Friedland, ref. 305. Many of the above articles are summarized in these 2 articles. Woeber, ref. 306, refers to Greenspan's paper above and states that thyroid hormone excess may lead to a decrease in bone mineral density in postmenopausal women).

b. **Hypercalcemia**:
Thyroid hormones directly stimulate osteoclasts to enhance bone resorption. This may result in mild hypercalcemia, with concomitant suppression of serum PTH levels, modest elevations in bone alkaline phosphatase and negative calcium balance (Cooper, ref. 62). When hypercalcemia occurs in a hyperthyroid patient, it is usually mild and it seems to be due to increased increased bone turnover (Burtis WJ and Stewart AF, ref. 50 and Potts, ref. 220).
The hypercalcemia of thyrotoxicosis is usually moderate but it should be considered in the differental of life-threatening hypercalcemia. Hypercalciuria is more common than hypercalcemia in thyrotoxic patients. Hyperphosphatemia and hyperphosphaturia may also occur (Mackovic-Basic M and Kleeman CR, ref. 168 and Loeb, ref. 165).
Thyroid hormones directly stimulate osteoclastic bone resorption, thereby inducing increases in serum levels and urinary excretion of calcium and phosphorous, increases in serum alkaline phosphatase and decreases in serum PTH levels (Mosekilde, references 189 and 190).

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, ref. 92).

d. **Reproductive:**
Overtreatment with levothyroxine may result in menstrual disturbances and impaired fertility (Stoffer, ref. 267).

VIII. DOSING AND ADMINISTRATION ISSUES IN ADULT AND PEDIATRIC PATIENTS:

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.

Levothyroxine dose requirements in adults with hypothyroidism:
Fish (ref. 91) reported that 112 $\pm$ 19 ug/day or 1.63 $\pm$ 0.42 ug/kg/day was the mean levothyroxine replacement dose (using Synthroid). Carr (ref. 53) also reported 1.6 ug/kg/day as the optimal T4 replacement dose.
Munson (ref. 192) 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, ref. 256):

- 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 (ref. 43), 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 (ref. 275), Munson (ref. 192) and Farewell and Braverman (ref. 87) 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.

Farewell and Braverman (ref. 87) state that after a change in levothyroxine dose, a new steady state will not be achieved for 4-6 weeks. They recommend that levothyroxine be instituted at 25 mcg/day in patients over 60 years with increments of 25 mcg every few months until the TSH is normalized. They recommend an initial dose of 12.5 mcg/day in patients with preexisting cardiac disease with increases of 12.5-25 mcg/day q 6-8 weeks, as indicated.

AHFS (ref. 6), Martindale (ref. 174) and Drug Evaluations (ref. 9) 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 (ref. 279) and Waldstein (ref. 295) 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 (ref. 295), states that patients with profound or long-standing hypothyroidism may initiate levothyroxine therapy at 50 ug/day.

Becker (ref. 18) 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 (ref. 303) recommends that elderly patients with heart disease receive 12.5-25 ug levothyroxine/day with dose adjustments at 4-6 week intervals.

Mazzaferri (ref. 176) 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 (ref. 71) 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 (ref. 306) 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.

Mandel (ref. 172) recommends full levothyroxine replacement doses (1.6 ug/kg/day) for healthy hypothyroid adults < 65 years of age. For patients ≥ 65 years of age or for patients with a history of cardiac disease, a starting dose of 25 ug/day of levothyroxine is recommended with increments of 25 ug at 8 week intervals until the serum TSH is normalized. For patients with central hypothyroidism, the levothyroxine dosing guidelines are as for patients with primary hypothyroidism. The possibility of secondary adrenal insufficiency should be considered in these patients, and, if present, glucocorticoid replacement should precede levothyroxine replacement. Mandel mentions that no contolled studies have been done that compare the efficacy of various degrees of TSH reduction consequent to the use of suppressive levothyroxine therapy on the course of either benign or malignant thyroid nodular disease. A trial of suppressive therapy is recommended in patients with a negative fine needle aspiration of a solitary, non-functioning nodule and with a normal or increased serum TSH level. For patients with non-toxic multinodular goiter with baseline serum TSH >1.0 mU/L, levothyroxine therapy may be given to suppress TSH to the 0.5-1.0 mU/L range. Continued suppressive therapy is recommended in these patients if the goiter decreases in size or remains stable, but serum TSH should be periodically monitored to monitor for the possible development of functional autonomy. With regard to goitrous autoimmune thyroiditis, patients often have high titers of thyroid antimicrosomal antibodies and are hypothyroid. The authors refer to a study by Hegedus (ref. 125), where the return to a normal serum TSH in these patients resulted in a mean decrease of 32% in thyroid volume, with almost 50% atttaining normal thyroid size after 2 years of therapy. Although it is accepted practice to suppress serum TSH to <0.1 mU/L in patients with differentiated thyroid cancer (which usually requires a leveothyroxine dose of 2.2-2.5 ug/kg/day), no studies have been done to evaluate the degree of TSH suppression which is necessary to inhibit potential tumor growth in these patients. The authors make the point that thyroid hormone accelerates bone turnover. They refer to studies which I summarize later in this review under Safety, Long-term Effects on Bone, in which bone loss and reductions in bone mineral density occurred in pre- and post-menopausal women receiving supraphysiological levothyroxine doses. The authors also state: "Even when the replacement dose is appropriately determined and monitored, it is still unclear whether women receiving levothyroxine replacement therapy are at an increased risk for decreased bone mineral density."