CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-301

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

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

Application #:	**21-301**	**Application Type:**	**NDA** **IND**
Sponsor:	**Jones Pharma, Inc.**	**Proprietary Name:**	**Levoxyl**
Investigator:		**USAN / Established Name:**	**Levothyroxine sodium**
Category:	**Thyroid hormone replacement**	**Route of Administration:**	**Oral**
Medical Reviewer:	**Jean Temeck,M.D.**	**Review Date:**	**5/4/01**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 28, 2000	July 31, 2000	NDA	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
[		]
October 19, 1999	NDA 21-210	Unithroid: Jerome Stevens Pharm.
[		]

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 article 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 Jones Pharma, Inc. 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: 5/4/01	
Medical Team Leader: /S/		Date:	

Executive Summary: /S/

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 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.

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 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 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. Although only representative articles from the literature pertaining to the use of levothyroxine in the pediatric population were included in the application, this reviewer, on her own, obtained the other references listed in the application's bibliography (some of which had been previously submitted by other sponsors). 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 Jones Pharma, Inc. 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.

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 Jones Pharma, Inc. 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 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. 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.

Note: Jones Pharma. Inc. states that Levoxyl has been commercially available for many years.

The following are the sponsor's proposed indications:

Dosage form and route of administration: tablets for oral administration

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. Qui, biopharmaceutics.

III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS:

See Dr. Qui'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 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.

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.

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

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.

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.

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.

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:

Drugs that decrease TSH secretion:

Dopamine

Glucocorticoids
Octreotide

Drugs that alter thyroid hormone secretion:
Decrease secretion:
- Lithium
- Iodide
- Amiodarone
- Aminoglutethimide

Increase secretion:
- Iodide
- Amiodarone

Drugs that decrease T4 absorption:
Colestipol
Cholestyramine
Colestipol/Niacin
Aluminum hydroxide
Ferrous sulfate
Sucralfate

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

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

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.

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.

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.

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:

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:

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 (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.

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 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.

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. Published literature referenced by the sponsor in their bibliography but not provided, was personally obtained by the reviewer.

Jones Pharma, Inc. has certified that they did not enter into any financial

arrangements with either the PI's or the subinvestigators of the bioavailability studies that would affect the outcome of these 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, it was assumed to be "grandfathered" as well.

Review of Efficacy:

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. However, Roti et al (Endocrine Reviews 14(4):401-423, 1993) 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 et al (Clin Endocrinol 35:235-238, 1991). 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 sugnificantly 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.

Roti et al (Endocrine Reviews 14(4):401-423, 1993) reviewed the efficacy of levothtroxine 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 (NEJM 331:174-180, 1994). 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 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).

A placebo-controlled trial conducted by Berghout et al (Lancet 336:193-7, 1990) 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 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. 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 in NEJM 338(20):1438-1447, 1998; Roti et al in Endocrine Reviews 14(4):401-423, 1993; Mandel et al in Ann Int Med 119:492-502, 1993; Singer et al in Arch Int Med 156:2165-2172, 1996; and Toft in NEJM 331:174-180, 1994). However, the target levels for TSH suppression in these conditions are generally higher than those recommended for thyroid cancer. Burch (Endocrinology and Metabolic Clinics of North America 24(4):663-710, 1995) 303, 1994 and Mandel (Ann Int Med 119:492-502, 1993) recommend that TSH be suppressed to 0.5-1.0 mU/L in patients with non-toxic multinodular goiter. Burch (Endocrinology and Metabolic Clinics of North America 24(4):663-710, 1995) and Gharib (Current Therapy in Endocrinology and Metabolism, 6th edition, ed. Bardin W, Mosley-Year Book, Inc., St. Louis, 1997, pp.1112-117) 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 (Werner and Ingbar's The Thyroid, 7th edition, ed.: Braverman and Utiger, Lippincott-Raven, Philadelphia, 1996, chapter 79, page 898; Roti et al in Endocrine Reviews 14(4):401-423, 1993; Hermus and Huysmans in NEJM 338(20):1438-47, 1998; Mandel et al in Ann Int Med 119:492-502, 1993; Singer et al in Arch Int Med 156:2165-2172, 1996; Toft in NEJM 331:174-180, 1994; and Farewell and Braverman:chapter 56: Thyroid and Antithyroid Drugs in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edition, New York, McGraw-Hill Press, 1996, pages 1383-1409). 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.

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 et al in Ann Int Med 119:492-502, 1993 and Ain in Endocrinology and Metabolic Clinics of North America 24(4):711-760, 1995). However, the level of TSH suppression to target may vary with tumor risk (low versus high). Singer et al (Arch Int Med 156:2165-2172, 1996) and Hershman and Gordon (Current Therapy in Endocrinology and Metabolism, 6th edition, ed. Bardin W, Mosley-Year Book, Inc., St. Louis, 1997, pp.122-126) recommend that TSH be suppressed below 0.01 mU/L in patients with high risk tumors. Toft (NEJM 331:174-180, 1994) provides a general recommendation of TSH suppression to <0.01 mU/L in patients with well differentiated thyroid cancer. In addition, Singer (same reference) mentions that the duration of suppression has not been established.

The importance of treating maternal hypothyroidism during pregnancy, even if mild, was highlighted by Haddow et al (NEJM 341:549-555, 1999). 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 et al (Clin Endocrinol 50:149-155, 1999) reported that children of women with free T_4 levels below the 5th and 10th 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 10th 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 et Al in Clin Endocrinology 14(4):401-423, 1993; Toft AD in NEJM 331(3):174-180, 1994; and Farewell and Braverman: chapter 56: Thyroid and Antithyroid Drugs, pp. 1383-1409, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edition, New York, McGraw-Hill Press, 1996), 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 _____ , 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 (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.

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VII. REVIEW OF SAFETY:

a. Review of Safety in the Bioavailability Studies:

Study No. 20646:

This bioavailability study was an open-label, single-dose, randomized, 2-way crossover comparing 300 ug Jones Pharma. levothyroxine tablets (dose 2 x 300 ug= 600 ug) to a Levothyroxine oral solution (prepared from Levothyroxine Sodium for Injection) in normal volunteers. Although 30 subjects received the solution, only 27 received the tablets. Reasons for study discontinuation in these 3 patients were: failing the drug screen (subject 6), personal reasons (subject 16) failing the check-in laboratory tests (subject 19). There were 18 treatment-emergent adverse events reported by 11/30 (37%) subjects. Headache was the most common adverse event following both treatments: 6 events on the tablets and 5 on the solution. The remaining adverse events were: on the tablets: 1 event of asthenia; on the solution: 1 event each of fever, malaise, dizziness, rhinitis, rash and dysmenorrhea. The majority of these AEs were mild or moderate in severity. None of the AEs were serious. On subject (#6) with a normal baseline ALT (35 U/L with normal range of 0-39 U/L) exhibited an ALT elevation to 207 U/L at the period 2 predose time point. This patient had only received the solution. No recheck was performed as this subject was dropped from the trial and subsequently lost to follow-up. Overall, no clinically significant changes were observed regarding vital signs, physical exam or clinical laboratory evaluations for either treatment.

Study No. 20655:

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 Levoxyl under fasting conditions in normal volunteers. Each dosage strength was administered in crossover fashion and in multiples to provide a single 600 mcg dose (12 x 50 mcg tablets, 6 x 100 mcg tablets, 3 x 300 mcg). 28 subjects were enrolled and 24 subjects completed the study. Reasons for study discontinuation in the 4 subjects were: failure to return for the last study period, a positive serum pregnancy test, serious AE of chest pain, and protocol non-compliance. 62 treatment-emergent adverse events (AEs) were reported by 17 (61%) of the 28 subjects. The incidence of AEs was similar across treatments. Headache was the most frequently reported adverse event (total of 17 AEs) followed by rhinitis (total of 6 events), nausea (5 events), increased cough and vomiting (4 events each), pain and lung disorder (3 events each). A total of 1-2 AEs were reported for each of the following: asthenia, chest pain, accidental injury, infection, tachycardia, diarrhea, dizziness, dry mouth, hypesthesia, bronchitis, dyspnea, pharngitis, sinusitis, rash, amblyopia, metorrhagia and unintended pregnancy. Only the episode of tachycardia was considered by the investigator to be possibly related to treatment. All other events were considered to be unrelated or unlikely related to study drug administration. The majority of reported AEs were mild in intensity. One subject (# 15) experienced a serious AE of severe, intermittent chest pain and mild dyspnea, considered by the investigator to be unrelated to treatment. These AEs occurred one day following dosing with 2 x 300 mcg tablets. Emergency room evaluation which included ECG and labs, was non-diagnostic. No trends were noted in vital signs (but the mean pulse rate increased by 14-18 bpm for all dosing regimend at the 5.83 hour time point),

clinical laboratory results or ECG's to suggest treatment-related differences. However, one subject (#27) experienced an elevated ALT (57 U/L with normal range of 0-50 U/L) at the 48 hour time point following 12 x 50 mcg dosing. Although the investigator requested a recheck, none was performed.

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 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.

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).

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 ≥ 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 (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.

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.

Jodar et al (Osteoporosis International 8:311-316, 1998) 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 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.

Schneider et al (JAMA 271(16):1245-49, 1994) 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 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.

(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) and Kooh et al (J Pediatr Endocrinol Metab 9:59-62, 1996) 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).

Reproductive:

Overtreatment with levothyroxine may result in menstrual disturbances and impaired fertility.

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 et al (NEJM 316:764-770, 1987) reported that 112 ± 19 ug/day or 1.63 ± 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.

Farewell and Braverman (chapter 56: Thyroid and Antithyroid Drugs in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edition, New York, McGraw-Hill Press, 1996, pages 1383-1409) 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, 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.

Mandel et al (Ann Int Med 1993; 119:492-502, 1993) 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 et al (Clin Endocrinol 1991;35:235-8), 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."

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; and Roti et al in Endocrine Reviews 14(4):401-423, 1993). 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 and Roti et al in Endocrine Reviews 14(4):401-423, 1993). 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 and Roti et al JCEM 81:1679-1682, 1996). Roti recommends that serum TSH be monitored at the end of the first trimester and every 2 months thereafter in pregnant women whose hypothyroidism is being treated with levothyroxine. 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 (ref. 1: Singer et al in JAMA 273:808-812, 1995; ref. 2: Farewell and Braverman chapter 56: Thyroid and Antithyroid Drugs in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edition, New York, McGraw-Hill Press, 1996, pages 1383-1409; ref. 3: The Thyroid and Its Diseases, 6th edition, ed.: De Groot, Larsen and Hennemann, Churchill Livingstone Inc., New York, New York, 1996; ref. 4: Williams Textbook of Endocrinology, 8th edition, edited by Jean Wilson and Daniel Foster, WB Saunders Co., Philadelphia, 1992, section 3: Thyroid, chapter 8, pages 357-4871992; and ref. 5: Current Therapy in Endocrinology and Metabolism, 6th edition, ed. C. Wayne Bardin, Mosby-Year Book, Inc., St. Louis, 1997, pp. 99). Although Roti et al (The Use and Misuse of Thyroid Hormone in Endocrine Reviews 1993, 14(4):401-423) states that the dose, frequency, route of administration, and type of thyroid hormone to be administered to patients with myxedema coma are debatable, the regimen he recommends entails initial administration of $T_4 \pm T_3$ by the intravenous route. Roti states that thyroid hormone may be administered orally or IV by the third day. He also refers to an article by Arlot et al (Intensive Care Med 17:16-18, 1991) in which patients with myxedema coma treated with either oral or iv T_4, were more likely to restore or elevate serum T_3 and T_4 concentrations after iv administration.