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1. INTRODUCTION TO THE NDA:

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

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

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

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

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

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

3 dosage strengths (50 mcg, 100 mcg and 300 mcg), each administered as a 600 mcg dose.

Note: Jerome Stevens has been marketing Unithroid in the U.S. for >8 years.

Proposed indications:

Levothyroxine sodium is currently used for the following indications:

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

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

Dosage form and route of administration: tablets for oral administration

2. EVALUATION OF SAFETY IN THE BIOAVAILABILITY STUDIES:

a. Study No. 254-98-134-3:

In this bioavailability study which compared tablets to an oral solution, there were 16 adverse events reported in 7/26 subjects (note: one subject reported AEs on both the tablets and oral solution). None of the AEs were serious. 6 AEs were reported on the tablets and 10 AEs were reported on the solution. On the tablets, 3 subjects reported 6 AEs (headache 3, abdominal "gurgling" 1, nausea 1 and cold sweats 1). On the oral solution, 5 subjects reported 10 AEs (headache 3, "cramp" frontal lobe 1, fatigue 1, dizziness 1, diarrhea 1, cold shivers 1, difficulty sleeping 1, and thick nasal mucus 1). All except one adverse event- headache- in 1 patient on the tablets, were regarded as unlikely or unrelated to the treatment administered. None of these AEs required treatment.

b. Study No. 254-98-135-2:

In this bioavailability study which compared 3 different tablet strengths, 49 AEs were reported in 16/29 subjects (note: AEs were reported on more than 1 dosage strength in 7 subjects). None of the AEs were serious. On the 50 mcg tablets, 20 AEs were reported in 11 subjects (headache 5, back/neck pain/ache 2, neck stiffness 2, lethargy/tired 2, epistaxis 1, body aches 1, vomiting 1, hot flashes 1, cough 1, sore throat 1, eye pressure & dryness 1, muscle spasms 1 and sleepiness 1). On the 100 mcg tablets, 15 AEs were reported in 6 subjects (headache 2, dry/burning eyes 4, body aches 1, anxiety 1, tired 1, throat

discomfort 1, nasal congestion 1, hot flushes 1, stomach cramps 1, diarrhea 1, and nausea/vomiting 1). On the 300 mcg tablets, 14 AEs were reported in 7 subjects (headache 3, cough 2, fever 1, chest pain 1, sore throat 1, sneezing 1, runny nose 1, fatigue 1, backache 1, abdominal pain 1 and vomiting 1). Only 3/49 AEs were rated as “possibly” related to the study drug (headache in 1 patient on the 100 mcg tablets and vomiting in 2 patients- one on the 100 mcg tablets and one on the 300 mcg tablets). All the other AEs were regarded as unrelated or unlikely to be related to the study drug. None of these 49 AEs required treatment.

3. REGULATION OF THYROID HORMONE SECRETION:

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

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

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.

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

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

5.A. Effects of thyroid hormones on metabolism:

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

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

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

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

5.C. Effects of thyroid hormones on maturation:

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

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

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

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

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

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

6. PHARMACOKINETICS:

6.A. Absorption:

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

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

Dietary fiber reduces the bioavailability of levothyroxine.

Fasting increases absorption of T4.

6.B. Distribution:

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

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

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

6.C. Volume of distribution:

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

6.D. Metabolism:

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

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

6.E. Elimination:

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

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

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

7. INDICATIONS AND USAGE:

Levothyroxine sodium is currently used for the following indications:

Hypothyroidism- As replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: cretinism, myxedema, non-toxic goiter (See PRECAUTIONS), 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.

8. CLINICAL SIGNS AND SYMPTOMS:

8.A. Hypothyroidism:

General:

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

CNS:

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

CV:

Bradycardia;

GI:

Constipation;

Dermatologic:

Dry skin, jaundice, coarseness or loss of hair;

Musculoskeletal:

Myalgias, muscle cramps;

Reproductive:

Irregular or heavy menses, infertility.

8.B. Hyperthyroidism or Overtreatment of Hypothyroidism:

General:

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

CNS:

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

CV:

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

Pulmonary:

Dyspnea

Ophthalmic:

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

GI:

Frequent bowel movements;

Dermatologic:

Hair loss;

Musculoskeletal:

Tremor and muscle weakness;

Reproductive:

Decreased menstrual flow and impaired fertility.

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

9. LABORATORY EVALUATION:

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

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

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

10. DOSE REQUIREMENTS:

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

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

Fish et al (NEJM 316:764-770, 1987) reported that 112 ± 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.

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

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

Waldstein (Thyroid Disease: Endocrinology, Surgery, Nuclear Medicine, and Radiotherapy, ed. S. Falk, Raven Press, Ltd., New York, 1990, chapter 17, pages 289-306), states that patients with profound or long-standing hypothyroidism may initiate levothyroxine therapy at 50 ug/day.

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

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

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

De Groot (The Thyroid and Its Diseases, 6th edition, ed.: De Groot, Larsen and Hennemann, Churchill Livingstone Inc., New York, New York, 1996) recommends the following regimen for patients with cardiac disease or severe long-standing hypothyroidism: a starting dose of 25 ug levothyroxine/day with increments of

25 ug every 8 weeks until the serum TSH normalizes. He notes that patients with severe long-standing hypothyroidism may develop psychoses or agitation during the initial phase of levothyroxine replacement therapy, therefore, lower initial replacement doses are recommended. DeGroot also states that if a patient is taking what is thought to be a full replacement dose of levothyroxine, but the serum TSH is found to be elevated, the levothyroxine dose should be increased in 12.5-25 ug increments and the serum TSH repeated in 8 weeks.

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

The underlying cause of thyroid disease may influence the levothyroxine dose requirement (Brent and Larsen in Werner and Ingbar's The Thyroid-see reference above). For example, patients with primary hypothyroidism caused by chronic autoimmune thyroiditis require slightly higher doses of T4 than patients with Graves' disease who are hypothyroid as a result of radioiodine therapy (Bearcroft et al, Clin Endocrinol 34:115, 1991). Among those with Graves' disease, the T4 replacement dose can vary as a function of not only the extent of antithyroid therapy but also the time since treatment. When levothyroxine is used to suppress TSH as in patients with thyroid cancer, the standard T4 suppressive dose is probably not less than 200 ug/day (Nilsson et al, Acta Med Scand 202:257, 1977). If subclinical hypothyroidism is treated, replacement levothyroxine doses generally range between 1.0-1.7 ug/kg/day. Per Mazzaferri (Am J Obstet Gynecol 176(3):507-514, 1997), the usual dose of levothyroxine for patients with subclinical hypothyroidism is 100 mcg/day. However, Mandel (Annals of Int Med 119(6):492-502, 1993) recommends a dose of 1 mcg/kg/day (50-75 mcg) levothyroxine to treat patients with subclinical hypothyroidism.

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

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

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

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

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

10.B. Levothyroxine dose requirements in pediatric patients:

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

- The average dose of levothyroxine at the start of treatment is 10-15 ug/kg/day with full replacement doses given to newborn infants.
- A lower starting dose of levothyroxine (e.g 25 ug/day) should be considered for infants with cardiac failure with an increase in dose in 4-6 weeks. Other adverse effects of levothyroxine such as hyperactivity in an older child can be minimized if the starting dose is one-fourth of the full replacement dose, and the dose is increased by one-fourth weekly until full replacement is reached.
- Infants with very low (<5 ug/dl) or undetectable serum T4 concentrations should begin to receive 50 ug daily.
- Secondary adrenal insufficiency must be considered when hypothyroidism is due to hypothalamic or pituitary disease. If adrenal insufficiency exists, glucocorticoid replacement should be initiated 2 days before T4 is started to avoid precipitating an acute adrenal crisis.
- The levothyroxine dose will need to be adjusted according to the infant's clinical response and determinations of serum T4 and TSH concentrations. The serum total T4 (corrected for variation in TBG levels) or free T4 should be maintained at all times in the upper half of the normal range and serum TSH suppressed into the normal range during the first 3 years of life. Some infants with congenital hypothyroidism, particularly in the early months of therapy, will have serum TSH levels in the 10-20 mU/L range (when it is optimal to maintain serum TSH below 10 mU/L), despite T4 levels in the upper half of the normal range. This elevated TSH appears to be the result of in utero hypothyroidism producing a resetting of the pituitary-thyroid feedback threshold. A failure of the serum T4 to increase into the upper half of the normal range by 2 weeks and/or the TSH to decrease below 20 mu/L within 4 weeks of initiation of levothyroxine administration, should alert the physician to the possibility that the child is not receiving adequate levothyroxine

regularly. At this point, careful inquiry should be made regarding compliance, dose of medication and method of administration.

- Serum T4 and TSH should be monitored with the following frequency:
 - a. at 2 and 4 weeks after the initiation of levothyroxine treatment
 - b. every 1 to 2 months during the first year of life
 - c. every 2 to 3 months between 1 and 3 years of age
 - d. every 3 to 12 months thereafter until growth is completed
 - e. at more frequent intervals when compliance is questioned or abnormal values are obtained.
 - f. Serum T4 and TSH and physical exam, if indicated, should be performed 2 weeks after any change in levothyroxine dosage.
- The infant should be watched during the first 2 weeks of levothyroxine therapy for cardiac overload, arrhythmias, and aspiration from avid suckling.
- Routine clinical examination, including assessment of growth and development, should be performed at regular intervals.
- Overtreatment for long periods of time has been associated with premature craniosynostosis and may adversely affect the tempo of brain maturation (minimal brain damage has been reported in children with thyrotoxicosis during infancy). Overtreatment will also accelerate bone age.
- When permanence of thyroid disease is not established, levothyroxine administration should be discontinued for 30 days, at some point after the child is 3 years of age. At that time, serum T4 and TSH levels should be obtained. If the T4 is low and the TSH is high, permanent hypothyroidism is confirmed and therapy is reinstated. If the T4 and TSH are normal, euthyroidism is assumed and a diagnosis of transient hypothyroidism is recorded. Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, one option when suspicion of permanence is high is to reduce the replacement dosage by half. If after 30 days, the serum TSH is elevated above 20 mU/L, the permanence of hypothyroidism is confirmed and full replacement therapy is resumed. However, if the serum TSH level has not risen, then treatment is discontinued for another 30 days with repeat serum T4 and TSH.

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

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

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

- a. an initial starting dose of 10-15 ug/kg/day of levothyroxine (or 50 ug/day in an average term infant of 3-4.5 kg), increases the serum T4 into the upper half of the normal range in 1-2 weeks. Serum TSH may be elevated above 20 mU/L despite serum T4 in the upper half of the

normal range in some infants with congenital hypothyroidism (CH) particularly during the early months of treatment. This is due to a resetting in utero of the feedback threshold for T4 suppression of TSH release in infants with CH.

- b. Therapy should be monitored, and individual T4 dose adjustments made, at 4-6 week intervals during the first 6 months, at 2-3 month intervals between 6-24 months of age, and at 3-6 month intervals thereafter. Assessments should include physical growth, motor development, bone maturation, and developmental progress at appropriate intervals. A Denver Developmental Screening Test or other screening tool may be useful to screen for developmental progress. More formal testing should be conducted when there is any suspicion of developmental delay and at 5-7 years of age.
- c. When hypothyroidism is secondary to hypothalamic or pituitary disease, it is essential to look for other hormone deficiencies: e.g. growth hormone and ACTH deficiency.

Fisher makes the following additional points in another article (Fisher : Acquired Juvenile Hypothyroidism in Werner and Ingbar's The Thyroid, 6th edition, ed. Braverman and Utiger, J.B. Lippincott Co., Philadelphia, 1991, pages 1228-1234):

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

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

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

0-6 months: 8-10 ug/kg/day
 6-12 mos.: 6-8 “
 1-5 yrs.: 5-6 “

6-12 yrs.: 4-5 “
 >12 yrs.: 2-3 “

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

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

11. DEMONSTRATION OF CLINICAL EFFECTIVENESS OF LEVOTHYROXINE:

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

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

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

12. SUMMARY OF SAFETY DATA:

12.A. Hypersensitivity reactions to levothyroxine products (probably to the dyes or tablet constituents) have been reported. The FDA has received several reports of hypersensitivity reactions including urticaria, pruritus, skin rash, flushing, angioedema,

various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing.

12.B. Pseudotumor cerebri has been reported in children receiving levothyroxine therapy.

12.C. End-organ effects:

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

12.D. Long-term Adverse Cardiovascular Effects:

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 (≥ 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.

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.

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

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

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

a. On Bone Mineral Density:

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 in both pre- and postmenopausal women with thyroid carcinoma.

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

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

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

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

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

Faber et al (Europ J of Endocrin 130:350-6, 1994) performed a meta-analysis of the results of 13 studies of bone density in several hundred

women who were receiving long-term (5-15 years) T4 treatment, most of whom had low serum TSH concentrations. Bone loss was measured in the distal forearm, femoral neck and lumbar spine. Premenopausal women, treated on average with 164 mcg L-T4/day for 8.5 years, had 2.67% less bone mass than controls (not statistically significant= NS), corresponding to an excess annual bone loss of 0.31% after 8.5 yrs. of treatment (NS). In contrast, postmenopausal women, treated on average with 171 mcg/day L-T4 for 9.9 yrs. had 9.02% less bone mass than controls, corresponding to a significant excess annual loss of 0.91% after 9.9 yrs. of treatment. Therefore, the meta-analysis did not find any statistically significant reduction in bone mass during prolonged L-T4 treatment in premenopausal women with reduced serum TSH. However, L-T4 treatment in postmenopausal women in doses leading to decreased serum TSH did result in significant excess annual bone loss compared to controls.

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

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

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.

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

13. DRUG-DRUG INTERACTIONS:

13.A. Drugs that decrease TSH secretion:

Dopamine
Glucocorticoids
Octreotide

13.B. Drugs that alter thyroid hormone secretion:

Decrease secretion:
Lithium
Iodide

Amiodarone
 Aminoglutcthimide
 Increase secretion:
 Iodide
 Amiodarone

13.C. Drugs that decrease T4 absorption:

Colestipol
 Cholestyramine
 Colestipol/Niacin
 Aluminum hydroxide
 Ferrous sulfate
 Sucralfate

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

Increased serum TBG concentration:

Estrogens
 Tamoxifen
 Heroin
 Methadone
 Mitotane
 Fluorouracil

Decreased serum TBG concentration:

Androgens
 Anabolic steroids (e.g. danazol)
 Nicotinic acid
 Glucocorticoids

Displacement from protein-binding sites:

Furosemide
 Fenclofenac
 Mefenamic acid
 Salicylates

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

Increased hepatic metabolism:

Phenobarbital
 Rifampin
 Phenytoin
 Carbamazepine

Decreased T4 5'-deiodinase activity:

Propylthiouracil
 Amiodarone
 Beta-adrenergic antagonist drugs
 Glucocorticoids

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

Digoxin:

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

Anticoagulants:

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

Antidiabetic agents (insulin and sulfonylureas):

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

13.G. Cytokines:

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

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

14. DRUG-DISEASE INTERACTIONS:

Disease states that affect levothyroxine requirements include:

a. Malabsorption (can increase dose requirements)

b. Disease states that alter serum TBG concentrations:

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

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

c. Concomitant cardiovascular disease:

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

d. Concomitant diabetes mellitus:

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

e. Concomitant adrenocortical insufficiency:

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

15. OVERDOSE:

Accidental or intentional acute or chronic overdose includes the signs and symptoms of thyrotoxicosis: palpitations, tachycardia, arrhythmias, increased blood pressure, chest pain, angina, shortness of breath, CHF, heat intolerance, increased sweating, fever, weight loss, vomiting, diarrhea, muscle weakness, periodic paralysis,

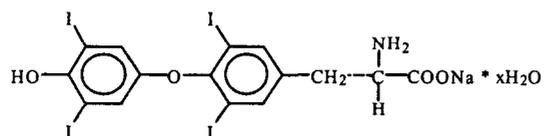
tremors, nervousness, irritability, anxiety, agitation, confusion, disorientation. Cerebral embolism, coma and death have been reported. Grand mal seizures were reported in a 30 month old boy who ingested 18 mg L-T₄ (Kulig et al JAMA 1985, 254:2109). Some patients have developed tolerance to the drug. The majority of the preparations ingested were either dessicated thyroid or levothyroxine. However, Hedberg (NEJM 316:993, 1987) reported palpitations, fatigue and tremor in individuals ingesting ground beef contaminated with thyroid.

16. Draft Class Labeling for Levothyroxine sodium:

The following class label for levothyroxine sodium was written by Dr. R. Steigerwalt, Pharm/Tox Team Leader, Dr. Steve Johnson (biopharm sections of the label), and myself (clinical sections). At my suggestion, the following article was used in writing the Drug-Drug Interactions section of the label: Drugs and Thyroid Function by M Surks and R Sievert, NEJM 333(25):1688-1694, 1995.

DESCRIPTION – (class content) – *Chemistry*

Levothyroxine sodium, USP tablets contain synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T₄) sodium]. Synthetic T₄ is identical to that produced in the human thyroid gland. Levothyroxine (T₄) sodium has an empirical formula of C₁₅H₁₀I₄N NaO₄ x H₂O, molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



Inactive Ingredients – (agent specific) – *Chemistry*

CLINICAL PHARMACOLOGY – (class content)

Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin-stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormone, L-thyroxine (T₄) and L-triiodothyronine (T₃), by the thyroid gland. Circulating serum T₃ and T₄ levels exert a feedback effect on both TRH and TSH secretion. When

serum T₃ and T₄ levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increase.

The mechanisms by which thyroid hormones exert their physiologic actions are not completely understood, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T₃ and T₄ diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins.

Thyroid hormones activate multiple metabolic processes essential to survival, normal growth and development, and normal maturation of the central nervous system and bone. Their metabolic actions include augmentation of cellular respiration and thermogenesis, and metabolism of proteins, carbohydrates and lipids. Their protein anabolic effects are essential to normal growth and development.

The physiologic actions of thyroid hormones are produced predominately by T₃, the majority of which (80%) is derived from T₄ deiodination in peripheral tissues.

PHARMACOKINETICS – (class content and agent specific – absorption)

Absorption – Absorption of orally administered T₄ from the GI tract ranges from 40% to 80%. The relative bioavailability of [drug name] tablets, compared to an equivalent dose of oral levothyroxine sodium solution, (is/are) approximately [X%]. The majority of the dose is absorbed from the jejunum and upper ileum. T₄ absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean formula. Dietary fiber decreases bioavailability of T₄. Absorption may also decrease with age. In addition, many drugs and foods affect T₄ absorption (see **DRUG-DRUG INTERACTIONS** and **DRUG-FOOD INTERACTIONS**).

Distribution – Greater than 99% of circulating thyroid hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The

higher affinity of both TBG and TBPA for T₄ partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T₄. Both protein-bound hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins (see **DRUG-DRUG INTERACTIONS** and **DRUG-LABORATORY TEST INTERACTIONS**). Thyroid hormones do not readily cross the placental barrier.

Metabolism – T₄ is slowly eliminated (see **TABLE 1**). Eighty-percent of circulating T₃ comes from peripheral T₄ monodeiodination. The liver is the major site of degradation for both T₄ and T₃; with T₄ deiodination also occurring at a number of additional sites, including the kidney and other tissues. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of the daily dose of T₄ is deiodinated to yield equal amounts of T₃ and rT₃. T₃ and rT₃ are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where it may be reabsorbed.

Elimination – Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T₄ is eliminated in the stool. Urinary excretion of T₄ decreases with age.

Table 1: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients				
Hormone	Ratio Released from Thyroid Gland	Biologic Potency	t _{1/2} (days)	Protein Binding (%) ²
Levothyroxine (T ₄)	20	1	6-7 ¹	99.96
Liothyronine (T ₃)	1	4	≤ 2	99.5
¹ 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism; ² Includes TBG, TBPA, and TBA				

INDICATIONS AND USAGE – (class labeling)

Levothyroxine sodium is used for the following indications:

Hypothyroidism – As replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: cretinism, myxedema, non-toxic goiter (see **PRECAUTIONS**), 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 from 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.

LABORATORY TESTS – Diagnosis and Monitoring

Diagnosis of hypothyroidism is confirmed by a sensitive TSH assay (second generation: sensitivity ≤ 0.1 mIU/L or third generation: sensitivity ≤ 0.01 mIU/L) and free-T₄.

Adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. Choice of laboratory tests depends on various factors including the etiology of the underlying thyroid disease; the presence of concomitant medical conditions, including pregnancy; and use of concomitant medications (see **DRUG-DRUG INTERACTIONS** and **DRUG-LABORATORY TEST INTERACTIONS**).

Due to thyroxine's long half-life, peak therapeutic effect upon initiation of levothyroxine therapy, may not be reached for 4-6 weeks.

Patients who are euthyroid but have positive microsomal antibodies are at risk for the development of hypothyroidism.

Pediatric – In pediatric patients with congenital or acquired hypothyroidism, adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free-T₄. Serum total- or free-T₄ should be maintained at all times in the upper half of the normal range in the first three years of life. Frequency of monitoring of these laboratory parameters is as follows: at 2 and 4 weeks after the initiation of treatment; every 1-2 months during the first year of life; every 2-3 months between 1 and 3 years of age; every 3 to 12 months thereafter until growth is completed. More frequent intervals of monitoring may be necessary if compliance is questioned or abnormal values are obtained. Serum T₄ and TSH, and physical exam, if indicated, should be performed 2 weeks after any change in levothyroxine dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals.

Adult – In adult patients with primary (thyroidal) hypothyroidism, serum TSH (using a sensitive assay) may be used alone to monitor therapy. Once the serum TSH has normalized, visits every 6-12 months are sufficient, depending on the clinical situation. A physical exam should be performed annually and a serum TSH measured at least annually. For patients who have recently started 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.

Secondary (pituitary) or Tertiary (hypothalamic) hypothyroidism – In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, serum TSH is not a reliable indicator of the adequacy of replacement therapy. In these conditions, it is necessary to monitor free-T₄. The serum free-T₄ level should be restored to the upper half of the normal range in these patients. Also, when secondary or tertiary hypothyroidism is present, a thorough endocrine evaluation is warranted to look for other pituitary hormone deficiencies (see **PRECAUTIONS**).

Subclinical hypothyroidism – This is characterized by a normal serum T₄ and an elevated serum TSH level.

Intracellular resistance to thyroid hormone – This is characterized by clinical hypothyroidism but an elevated serum T₄.

CONTRAINDICATIONS – (class labeling)

Levothyroxine is contraindicated in patients with untreated thyrotoxicosis of any etiology and in acute myocardial infarction. It is also contraindicated in patients with hypersensitivity to thyroid hormones or any of the inactive tablet ingredients. Levothyroxine is also contraindicated in patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see **PRECAUTIONS**).

WARNINGS: Thyroid hormones, either alone or with other therapeutic agents, should not be used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

The use of levothyroxine sodium in the treatment of obesity, either alone or in combination with other drugs, is unjustified. The use of levothyroxine sodium is also unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

PRECAUTIONS – (class labeling)

In infants and children, overtreatment with levothyroxine may result in craniosynostosis, disrupt the tempo of brain maturation and accelerate the bone age, with resultant premature closure of the epiphyses and compromised adult height.

In women, long-term levothyroxine sodium therapy has been associated with decreased bone mineral density, especially in postmenopausal women who are overreplaced or who are receiving suppressive doses of levothyroxine sodium. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimal dose necessary to achieve the desired clinical and biochemical response.

Exercise caution when administering levothyroxine to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. Initiate levothyroxine therapy at lower doses than that used in younger individuals or in patients without cardiac disease (see **DOSAGE AND ADMINISTRATION**). If cardiac symptoms develop or worsen, reduce the dose of levothyroxine. Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness and cardiac contractility and may precipitate angina or arrhythmias. Closely observe patients with coronary artery disease during surgery, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of thyroid hormone and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Exercise caution when administering levothyroxine to patients with autonomous thyroid tissue. The effects of exogenous thyroid hormone administration will be additive to that produced endogenously, and, thereby may precipitate thyrotoxicosis.

The physician should be alert to the association of hypothyroidism with certain medical conditions. Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, with cardiovascular anomalies (pulmonary stenosis, atrial septal defect and ventricular septal defect) being the most common association. In patients with secondary or tertiary hypothyroidism, the possibility of secondary adrenal insufficiency should be considered, and, if diagnosed, treated with glucocorticoids prior to initiation of treatment with levothyroxine sodium (see **PRECAUTIONS**). Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia and insulin-dependent diabetes mellitus (autoimmune polyglandular syndrome).

Levothyroxine sodium therapy in patients with concomitant diabetes mellitus or insipidus, or adrenal insufficiency may exacerbate the symptom intensity. Adjustments in the therapy of these concomitant endocrine diseases may be required; most notably an increase in antidiabetic drug requirements, and initiation of glucocorticoid treatment prior to that of levothyroxine to avoid precipitation of an acute adrenal crisis (see **DRUG-DRUG INTERACTIONS**).

Thyroxine increases the response to anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant therapy may be warranted with correction of the hypothyroid state or when the levothyroxine dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see **DRUG-DRUG INTERACTIONS**).

The therapeutic effects of digitalis may be reduced by thyroid hormone. Serum digitalis levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis.

Seizures have been reported rarely with the institution of levothyroxine therapy.

Many drugs and foods may affect levothyroxine absorption, secretion, transport and metabolism and, therefore, require adjustments in dosing (see **DRUG-DRUG INTERACTIONS and DRUG-FOOD INTERACTIONS**).

Patient Information

1. Notify your doctor if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding or are taking any other medications including prescription and over-the-counter preparations.
2. Notify your doctor of any other medical conditions you may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems. Your dose of medications used to control these other conditions may need to be adjusted while you are taking levothyroxine. If you have diabetes, monitor your blood and/or

urinary glucose levels as directed by your doctor and immediately report any changes to your doctor. If you are taking blood thinners, your clotting status should be checked frequently.

3. Use levothyroxine only as prescribed by your doctor. Do not discontinue or change the amount you take or how often you take it, unless directed to do so by your doctor.
4. Levothyroxine sodium is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient hypothyroidism, usually associated with an inflammation of the thyroid gland (thyroiditis).
5. Take levothyroxine as a single dose, preferably on an empty stomach, one-half to one hour before breakfast. Levothyroxine absorption is increased on an empty stomach.
6. It may take several weeks before you notice an improvement in your symptoms.
7. Notify your doctor if you experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, heat intolerance, fever, changes in menstrual periods, hives or skin rash or any other unusual medical event.
8. Notify your doctor if you become pregnant while taking levothyroxine. It is likely that your dose of levothyroxine will need to be increased while you are pregnant.
9. Notify your doctor or dentist that you are taking levothyroxine prior to any surgery.
10. Partial hair loss may occur rarely during the first few months of levothyroxine therapy, but this is usually temporary.
11. Levothyroxine should not be used as a primary or adjunctive therapy in a weight control program.
12. Keep levothyroxine out of the reach of children. Store levothyroxine away from heat, moisture and light.

Drug Interactions

Drug-Drug Interactions – Drug-drug interactions are influenced by variables such as gender, race, age, concurrent illness and thyroid status. For example, failure to administer glucocorticoids in hypothyroid patients with concomitant adrenocortical

insufficiency, may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone (see **PRECAUTIONS**).

Levothyroxine sodium should be administered at least 4 hours apart from drugs that interfere with its absorption.

Any agent that alters thyroid hormone synthesis, secretion, transport, metabolism, or target tissue response, may alter the therapeutic response of levothyroxine sodium. Refer to table 2 for representative examples of drug interactions with levothyroxine sodium.

Consult appropriate references for additional drug-drug interactions.

Table 2: Drugs Which May Interfere With Thyroid Hormone Therapy	
Drug or Drug Class	Effect
Reduced TSH Secretion – but not sustained; therefore, hypothyroidism does not occur	
Dopamine / Dopamine Agonists Glucocorticoids Octreotide	Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: Dopamine ($\geq 1 \mu\text{g}/\text{kg}/\text{min}$); Glucocorticoids (hydrocortisone $\geq 100 \text{ mg}/\text{day}$ or equivalent); Octreotide ($> 100 \mu\text{g}/\text{day}$).
Drugs that Alter Thyroid Hormone Secretion	
Decreased thyroid hormone secretion which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodide (including iodine-containing Radiographic contrast agents) Lithium Methimazole Propylthiouracil (PTU) Sulfonamides Tolbutamide	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients.
Increased thyroid hormone secretion which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing Radiographic contrast agents)	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Reduced T_4 absorption which may result in hypothyroidism	
Antacids - Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Cation Exchange Resins - Kayexalate Ferrous Sulfate Sucralfate	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least 4 hours apart from these agents.
Altered T_4 and T_3 Serum Transport – but FT_4 concentrations remain normal; and, therefore, the patient remains euthyroid	
Increased serum TBG concentration	Decreased serum TBG concentration
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane	Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid

Tamoxifen	
Protein-binding site displacement	
Furosemide (> 80 mg IV) Heparin Hydantoin NSAIDs (non-steroidal anti-inflammatory drugs) - Fenamates - Phenylbutazone Salicylates (> 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in FT ₄ . Continued administration results in a decrease in serum T ₄ , and normal FT ₄ and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T ₄ and T ₃ to TBG and transthyretin. An initial increase in serum FT ₄ , is followed by return of FT ₄ to normal levels with sustained therapeutic serum salicylate concentrations, although total-T ₄ levels may decrease by as much as 30%.
Altered T₄ and T₃ Metabolism	
Increased hepatic metabolism which may result in hypothyroidism	
Carbamazepine Hydantoin Phenobarbital Rifampin	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of thyroxine, resulting in increased thyroxine requirements. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total- and free-T ₄ may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.
Decreased T₄ 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists - (e.g., Propranolol > 160 mg/day) Glucocorticoids - (e.g., Dexamethasone ≥ 4 mg/day) Propylthiouracil (PTU)	Administration of these enzyme inhibitors decrease the peripheral conversion of T ₄ to T ₃ , leading to decreased T ₃ levels. However, serum T ₄ levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (> 160 mg/day), T ₃ and T ₄ levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T ₃ concentrations by 30% with minimal change in serum T ₄ levels. However, long-term glucocorticoid therapy may result in slightly decreased T ₃ and T ₄ levels due to decreased TBG production (see above).
Miscellaneous	
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	Thyroxine hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.
Antidepressants - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline)	Concurrent use of tricyclic antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - Insulin	Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.
Cardiac Glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.
Cytokines - Interferon- α - Interleukin-2	Therapy with interferon- α has been associated with the development of antithyroid microsomal antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients. Interferon- β and - γ have not been reported to cause thyroid dysfunction.
Growth Hormones - Somatrem - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators - (e.g., Theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic Agents	Thyroid hormones may reduce the uptake of ¹²⁵ I, ¹³¹ I, and ^{99m} Tc.
Sympathomimetics	Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine	These agents have been associated with thyroid hormone and / or TSH level alterations by various mechanisms.

Nitroprusside Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	
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Drug-Food Interactions – Soybean flour (infant formula), cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the GI tract.

Drug-Laboratory Test Interactions – Changes in TBG concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone or the FT₄I. Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

Medicinal or dietary iodine will reduce radioiodine uptake. Therefore, iodine supplements should be temporarily withheld to maximize a diagnostic or therapeutic dose of radioiodine.

Persistent clinical and laboratory evidence of hypothyroidism despite an adequate replacement dose of levothyroxine indicates either inadequate absorption, poor compliance, drug interactions or decreased T_4 potency (see **DRUG-DRUG INTERACTIONS**).

Carcinogenesis, Mutagenesis, and Impairment of Fertility – Studies with [drug name] have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility. The synthetic T_4 [in tradename] is identical to that produced naturally by the human thyroid gland. Although there has been a reported association between prolonged thyroid hormone therapy and breast cancer, this has not been confirmed.

Patients receiving levothyroxine sodium for established indications should not discontinue therapy.

Pregnancy – Category A – Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Therefore, the possibility of fetal harm appears remote. However, because studies cannot exclude the possibility of harm, levothyroxine sodium should be used during pregnancy only if needed.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. Therefore, levothyroxine sodium should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be treated. During pregnancy, serum T4 levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women taking levothyroxine sodium should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of levothyroxine sodium. Since postpartum TSH levels are similar to preconception values, the levothyroxine dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-8 weeks postpartum.

Thyroid hormones cross the placental barrier to some degree as evidenced by levels in cord blood of athyrotic fetuses being approximately one-third maternal levels. However, transfer of thyroid hormone from the mother to the fetus may not be adequate to prevent *in utero* hypothyroidism.”

Nursing Mothers – Since thyroid hormones are excreted minimally in human milk, caution should be exercised when [drug name] is administered to a nursing woman. However, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.

Pediatric Use –

Congenital Hypothyroidism – Rapid restoration of normal serum T₄ concentrations is essential for preventing the adverse effects of neonatal hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, levothyroxine therapy should be initiated immediately upon diagnosis and is generally continued for life. The goal of treatment is to achieve and maintain normal mental and physical growth and development.

The initial dose of levothyroxine varies with age and body weight (see **DOSAGE AND ADMINISTRATION**). Full replacement doses may be given initially except in infants and children with underlying cardiac disease in whom a lower dose is initially used followed by gradual upward titration. One should aim to constantly maintain the serum total- or free-T₄ in the upper half of the normal range in the first 3 years of life. While the aim of therapy is to also normalize the serum TSH level, this is not always possible in a small percentage of patients, particularly in the first few months of therapy due to a resetting of the pituitary-thyroid feedback threshold as a result of *in utero* hypothyroidism. Failure of the serum T₄ to increase into the upper half of the normal range within 2 weeks of initiation of levothyroxine therapy, and/or the serum TSH to decrease below 20 mU/L within 4 weeks, should alert the physician to the possibility that the child is not receiving adequate levothyroxine regularly. Careful inquiry should then be made regarding compliance, dose of medication and method of administration. The infant should be monitored during the first 2 weeks of levothyroxine therapy for cardiac overload, arrhythmias and aspiration from avid suckling.

Serum total- or free-T₄ and TSH should be monitored at frequent intervals (see **LABORATORY TESTS – DIAGNOSIS AND MONITORING**). In addition, clinical examination, and assessment of growth and physical and mental development, as well as bone age, should be performed at regular intervals.

While it is critical to avoid undertreatment and the subsequent deleterious effects on mental development and linear growth, it is also important to avoid overtreatment.

Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

The physician should evaluate the patient for other endocrine deficiencies when hypothyroidism is due to hypothalamic or pituitary disease. If there is concomitant adrenal insufficiency, glucocorticoid replacement therapy should be initiated two days before levothyroxine therapy is started to avoid precipitating an acute adrenal crisis.

When permanence of thyroid disease is not established, levothyroxine administration should be discontinued for 30 days only after the child is 3 years of age. Serum T_4 and TSH levels are then obtained. If the T_4 is low and the TSH high, the permanence of the hypothyroidism has been established, and levothyroxine therapy is reinstated. If the T_4 and TSH are normal, euthyroidism is assumed and, therefore, the hypothyroidism was transient. In this instance, however, the physician should carefully monitor the child and repeat the thyroid function tests at the slightest suspicion of relapse. If the results of the levothyroxine withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, one option when suspicion of permanence is high, is to reduce the replacement dose by half. If, after 30 days, the serum TSH is elevated above 20 mU/L, the permanence of the hypothyroidism is confirmed and full replacement therapy is resumed. However, if the serum TSH has not risen, then treatment is discontinued for another 30 days followed by repeat serum T_4 and TSH.

Acquired Hypothyroidism in Pediatric Patients— The goal of treatment is the same as that for congenital hypothyroidism: to achieve and maintain normal mental and physical growth and development.

The initial dose of levothyroxine varies with age and body weight (see **DOSAGE AND ADMINISTRATION**). In general, children may be started on full replacement doses.

Lower initial doses may be used if there is underlying cardiac disease or in children with severe, long-standing hypothyroidism. Also, the adverse effects of levothyroxine such as hyperactivity in an older child can be minimized if the starting dose is one-fourth of the full replacement dose, and the dose is increased by one-fourth weekly until full replacement is reached.

An approach similar to the one for congenital hypothyroidism is taken for evaluating and monitoring the child with acquired hypothyroidism. Treated children may manifest a transient period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

As with congenital hypothyroidism, both undertreatment and overtreatment are to be avoided. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Permanence of hypothyroidism may be assessed by levothyroxine withdrawal as described above for congenital hypothyroidism.

ADVERSE REACTIONS

Adverse reactions are primarily those of hyperthyroidism due to therapeutic overdosage.

They include the following:

General: fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating;

Central nervous system: headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia;

Musculoskeletal: tremors, muscle weakness;

Cardiac: palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest;

Pulmonary: dyspnea;

GI: diarrhea, vomiting and abdominal cramps;

Dermatologic: hair loss;

Reproductive: menstrual irregularities and infertility.

Pseudotumor cerebri has been reported in children receiving levothyroxine therapy.

Inadequate levothyroxine dosage will produce or fail to resolve symptoms of hypothyroidism.

Hypersensitivity reactions may occur. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing.

OVERDOSAGE

The signs and symptoms of overdose are those of hyperthyroidism (see **ADVERSE REACTIONS**). In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma and death have been reported. Seizures have occurred in children. Symptoms may not necessarily be evident or may not appear until several days after ingestion of levothyroxine sodium.

Overreplacement of levothyroxine or overtreatment over a prolonged period in pediatric patients may lead to craniosynostosis in infants, may adversely affect the tempo of brain maturation, and accelerate bone age with resultant premature closure of the epiphyses and compromised adult stature in children.

Overreplacement of levothyroxine sodium in adult patients has been associated with decreased bone mineral density, particularly in postmenopausal women. Levothyroxine overreplacement may also have adverse cardiovascular effects such as increased heart rate and precipitation of angina or arrhythmias.

Treatment of Overdosage – Reduce the dose of levothyroxine or temporarily discontinue the drug. Reinstitute therapy at a lower dose.

Acute Massive Overdosage – This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. If not contraindicated (e.g. by seizures, coma or loss of the gag reflex), empty the stomach by emesis or gastric lavage to decrease gastrointestinal absorption. Activated charcoal or cholestyramine may also be used to decrease absorption. Counteract central and peripheral increased sympathetic activity by administering B-receptor antagonists, especially propranolol (1 to 3 mg IV over a 10 minute period, or orally, 80 to 160 mg/day). Provide respiratory support as needed; control congestive heart failure with cardiac glycosides; control fever, hypoglycemia and fluid loss as necessary. Glucocorticoids may be given to inhibit the conversion of T_4 to T_3 . Because T_4 is highly protein bound, very little drug will be removed by dialysis.

DOSAGE AND ADMINISTRATION

The dose of levothyroxine is dependent on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant illnesses (see **PRECAUTIONS**) and medications (see **DRUG-DRUG INTERACTIONS**), the etiology of the hypothyroidism and the severity and duration of hypothyroid symptoms. The following recommendations serve only as dosing guidelines for levothyroxine which must be individually titrated to the needs of the patient based on clinical response and laboratory parameters. The goal of replacement therapy is to achieve and maintain a euthyroid state clinically and biochemically. The goal of suppressive therapy is to inhibit growth and function of abnormal thyroid tissue.

Levothyroxine is administered as a single daily dose, preferably one-half to one-hour before breakfast. Levothyroxine should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (see **DRUG-DRUG INTERACTIONS**).

In patients with concomitant adrenal insufficiency, initiate glucocorticoid replacement prior to levothyroxine therapy to avoid precipitating an acute adrenal crisis (see **PRECAUTIONS**).

Hypothyroidism in Adults and in Children in Whom Growth and Puberty is Complete—

The average full replacement dose of levothyroxine is approximately 1.7 mcg/kg/day. Older patients may require less than 1 mcg/kg/day. Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have been recently treated for hyperthyroidism or with hypothyroidism for only a short time (such as a few months). A single oral dose is usually taken in the morning, one-half to one hour before breakfast.

For most other patients older than 50 years or young patients with underlying cardiac disease, an initial starting dose of 25-50 mcg levothyroxine daily is recommended, with gradual increments in dose at 6-8 week intervals.

The starting dose of levothyroxine in elderly patients with cardiac disease may be only 12.5-25 mcg/day, with gradual increments at 4-6 week intervals.

Clinical and laboratory evaluations should be performed before dosing adjustments are made (see **LABORATORY TESTS – DIAGNOSIS AND MONITORING**). The levothyroxine dose is generally adjusted by 12.5-25 mcg increments, until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH is normalized. If cardiac symptoms develop or worsen, the cardiac disease should be evaluated and the levothyroxine dose should be reduced or withheld for one week and restarted at a lower dose. In patients with secondary or tertiary hypothyroidism, the levothyroxine dose is adjusted until the patient is clinically euthyroid and the serum free-T₄ level is restored to the upper half of the normal range.

In patients with severe hypothyroidism, initiate levothyroxine therapy at 12.5-25 mcg/day with increases of 25-50 mcg/day every 2-4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized. Lower initial doses are

recommended in these patients to avoid precipitation of psychosis and agitation during the initial phase of levothyroxine therapy.

Pregnancy may increase levothyroxine requirements (see **PREGNANCY**).

If subclinical hypothyroidism is treated, lower levothyroxine doses (e.g. 1 mcg/kg/day) than that used for full replacement may be adequate to normalize the serum TSH level. Patients who are not treated should be monitored yearly for changes in clinical status and thyroid laboratory parameters.

Since levothyroxine over-replacement has been associated with reduced bone mineral density, particularly in post-menopausal women, it is recommended that the minimal dose be administered that will achieve the desired clinical and biochemical response.

When optimal replacement has been attained, clinical and biochemical monitoring may be performed every 6-12 months, depending on the clinical situation and whenever there is a change in the patient's status (see **LABORATORY TESTS – DIAGNOSIS AND MONITORING**).

Levothyroxine doses greater than 200 mcg/day are seldom required. An inadequate response to daily doses \geq 300 mcg/day is rare and may indicate poor compliance, malabsorption and/or drug interactions.

Myxedema Coma – Myxedema coma is a life-threatening emergency. LEVOTHYROXINE SODIUM FOR INJECTION is recommended because poor circulation and hypometabolism may result in unpredictable absorption of levothyroxine sodium from other than the intravenous route.

TSH Suppression in Well-differentiated Thyroid Cancer and Thyroid Nodules – In general, the levothyroxine dose is higher when used as suppressive rather than replacement therapy. No controlled clinical studies have compared different degrees of TSH suppression in the treatment of benign or malignant thyroid nodules.

Levothyroxine is used as an adjunct to surgery and radioiodine therapy in the treatment of well-differentiated (papillary and follicular) thyroid cancer. Generally, TSH is suppressed to <0.1 mU/L, and this usually requires a levothyroxine dose of greater than 2 mcg/kg/day.

The efficacy of TSH suppression in the treatment of benign thyroid nodules is controversial. Therefore, the dose used for TSH suppression should be individualized to the specific clinical circumstances, weighing the potential benefits of treatment against the risks of inducing iatrogenic hyperthyroidism. Generally, the smallest dose of levothyroxine should be administered to achieve the targeted clinical response. If levothyroxine treatment is initiated, the goal is generally suppression of TSH to a higher target level (0.1-0.3 mU/L) than that used for the treatment of thyroid cancer. Levothyroxine may also be used to treat patients with nontoxic multinodular goiter who have a TSH in the normal range, to suppress TSH to 0.1-0.3 mU/L.

Levothyroxine should be administered with caution to patients with autonomous thyroid tissue to prevent precipitation of thyrotoxicosis (see **PRECAUTIONS**).

Pediatric Dosage – Congenital or Acquired Hypothyroidism – The dose of levothyroxine is dependent on a variety of factors including the patient's age, weight and cardiovascular status. In general, levothyroxine therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's mental and physical growth and development (see **PEDIATRIC USE – CONGENITAL and ACQUIRED HYPOTHYROIDISM**). A single oral dose is usually given in the morning, one-half to one hour before administering food.

Initiate full levothyroxine therapy in newborn infants at 10-15 mcg/kg/day. A lower starting dose (e.g., 25 mcg/day) should be considered in infants at risk for cardiac failure with an increase in dose in 4-6 weeks. Infants with very low (< 5 mcg/dl) or undetectable serum T₄ concentrations should begin to receive 50 mcg levothyroxine per day. If

concomitant adrenal insufficiency exists, initiate glucocorticoid replacement 2 days prior to levothyroxine therapy to avoid precipitating an acute adrenal crisis.

The infant should be monitored closely during the first 2 weeks of levothyroxine therapy for cardiac overload, arrhythmias and aspiration from avid suckling.

As with newborn infants, levothyroxine therapy is usually initiated at full replacement doses in all other pediatric age groups, with the recommended dose per body weight decreasing with age (see **TABLE 3**). However, in children with chronic or severe hypothyroidism, an initial dose of 25 mcg levothyroxine per day is recommended with increments of 25 mcg every 2-4 weeks until the desired effect is achieved.

Hyperactivity in an older child can be minimized if the starting dose is one-fourth of the full replacement dose, and the dose is increased by one-fourth weekly until full replacement is reached.

Adjustments in levothyroxine dose will be based on clinical response, including assessment of mental and physical growth and development and bone maturation, as well as laboratory determinations of serum T₄ and TSH concentrations (see **LABORATORY TESTS – DIAGNOSIS AND MONITORING and PEDIATRIC USE – CONGENITAL and ACQUIRED HYPOTHYROIDISM**). Avoid undertreatment and overtreatment.

Levothyroxine tablets may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5-10 ml or 1-2 teaspoons) of water. This suspension can be administered by spoon or dropper. **DO NOT STORE THE SUSPENSION**. Foods that decrease absorption of levothyroxine such as soybean infant formula should not be used for administering levothyroxine.

Table 3: Levothyroxine Dosing Guidelines for Pediatric Hypothyroidism	
AGE	Daily Dose Per Kg Body Weight^a
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
>12 years	2-3 mcg/kg/day
Growth and puberty complete	~1.7 mcg/kg/day

^a The dose should be adjusted based on clinical response and laboratory parameters (see **LABORATORY TESTS – DIAGNOSIS AND MONITORING**).

HOW SUPPLIED**STORAGE** – (agent specific) – *chemistry***Rx ONLY****MANUFACTURER****17. Evaluation and Regulatory Action:**

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

In addition, a 25 mcg dosage strength that meets chemistry and biopharm criteria for approval, is essential for proper labeling of the product for safe and

effective use given that in certain clinical situations, levothyroxine sodium dosing is initiated at 12.5-25 mcg/day and increased in 12.5-25 mcg dosing increments.

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

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cc. NDA Arch 21,137; 21,116 and 21,118
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Note: A draft algorithm for pediatric formulations is appended. This draft was written by the Pediatric Formulations Working Group and was disseminated at the July, 13, 2000 Pedicomm meeting.

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cc. NDA Arch 21,210
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 HFD-510: Dr. Ahn, Dr. Johnson, Dr. Steigerwalt and Mr. McCort