CENTER FOR DRUG EVALUATION AND RESEARCH

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Medical Review(s)

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NDA # 21,137
Levolet (levothyroxine sodium) tablets
Vintage Pharmaceuticals, Inc.
Date submitted: April 30, 1999
Date of review: February 19, 2000

Medical Team Leader review of NDA

Background

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

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

The Levolet NDA is the first NDA for a levothyroxine-containing oral drug product submitted following on the August 1997 FR notice.

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

For the uses described above, T4 is safe and effective, but only when it is used in doses that maintain levels of circulating T4 and TSH within the range of normal. For these indications, it serves to supplement or substitute for endogenously produced T4, a hormone (as it is converted to T3) that, as stated above, is essential for life.

This does not imply that any currently available levothyroxine-containing oral drug product is safe and effective. Indeed, because of instances of failure of available products to maintain potency through the expiration date, because of lot-to-lot inconsistencies in the amount of active ingredient present in tablets of the same nominal dosage strength,

problems related to both safety and efficacy have arisen. Chronic underdosing with T4 as well as both acute and chronic overdosing with T4 can have serious health consequences. Thus, only high-quality T4-containing products will be both safe and effective.

The current drug product, Levolet, contains, in addition to graded quantities of T4, potassium iodide — mcg/tablet, ——. From a clinical standpoint, the content of KI presents the only safety issues with this product.

Safety of Levolet in light of its content of KI and ramifications for recommendations regarding its use

Dr. Temeck has exhaustively reviewed the literature in her review of 2-11-00. This review is for the most part a summary of information contained in her review.

Iodide has effects on thyroid function that depend upon dose, age of the individual, presence or absence of underlying thyroid disease, iodine status (sufficient or deficient), and use of concomitant medications. These effects include suppression of thyroid function (Wolff-Chaikoff, iodide-induced hypothyroidism) and stimulation of thyroid function (iodide induce hyperthyroidism or thyrotoxicosis).

In general, large doses of iodine have been implicated in these phenomena. However, isolated cases and a small number of studies have demonstrated potential adverse effects on thyroid function of microgram doses of iodide.

Because most of the use of T4-containing drug products is for the purposes of thyroid hormone replacement in hypothyroidism, any tendency toward thyroid suppression due to the iodide content of Levolet is of no clinical consequence in such patients. Indeed, because exogenously administered T4 will suppress pituitary TSH release and remove any stimulus for iodide uptake and subsequent T4 synthesis by the gland, it follows that, to the extent that it matters at all, any direct effect of the iodide on thyroid function will be diminished. In short, in hypothyroid patients taking Levolet, there are no issues raised by the KI content of the product.

The iodide content of Levolet is, however, of concern in three instances.

1. **Fetus and nursing infant.** In contrast to T4, iodide readily crosses the placenta and is secreted in milk. The fetal and neonatal thyroids are extremely active metabolically, avidly take up iodine, and are more sensitive than the mature thyroid to the suppressive effects of iodide. In the fetus and the nursing infant, any adverse effects of such thyroid suppression will <u>not</u> be mitigated by the T4 in Levolet. The risks of *in utero* or neonatal hypothyroidism are obviously significant, particularly for brain and overall nervous system development. While the upper limit of safe intake of iodide by either pregnant or nursing mothers is not known, transient neonatal hypothyroidism has been described in one child whose mother took prenatal vitamins containing 150 mcg iodine throughout pregnancy. Furthermore, depending on iodine status (deficient or sufficient), as little as 200 mcg daily has been shown to suppress thyroid function in premature infants.

2. **Patients at risk for iodide-induced thyrotoxicosis.** While this is rare in the U.S. because of the absence of any areas of iodine deficiency, nevertheless, patients with goiter (potentially due to iodine deficiency) or nodular thyroid disease may be at increased risk for iodide-induced hyperthyroidism. Particularly in elderly patients with underlying heart or cerebrovascular disease, this may pose a risk for adverse clinical outcomes as angina, arrhythmia, heart attack, sudden death, or stroke.

3. **Patients receiving radioiodine for diagnostic or therapeutic purposes.** In order to maximize uptake of radioiodine for diagnostic scanning or for ablation of well-differentiated cancer or Graves' disease (hyperthyroidism), dietary iodine intake as well as that contained in Levolet should be restricted. Withholding T4 therapy for 1 week, as suggested by Dr. Temeck, is unlikely to have any symptomatic or clinically significant effects on patient well-being.

Summary and conclusions

The safety and effectiveness of T4 itself are not in question as replacement or substitution for endogenously synthesized T4. Safe and effective use of T4 products requires that such products be of high quality such that consistent dosing may be effected within lots throughout the labeled shelf life and across lots over time. This obviates the risks associated with underdosing or overdosing on either an acute or chronic basis.

Levolet contains — mcg of KI per tablet, across the dosage range. Because the majority of patients taking Levolet will be using it to supplement or replace endogenous T4 in the setting of a failing thyroid gland, any risk of the KI to suppress thyroid function will be moot, effectively mitigated by the T4 content of the pill, the reason for taking it in the first place.

In the fetus and nursing infant, iodide reaching the thyroid via placental passage or mother's milk will not be accompanied by exogenous T4. While the safe upper limit for maternal iodine intake has not been established, there are data to suggest a small risk of hypothyroidism to the fetus and nursing infant with intake of small (hundreds of mcg) quantities of KI by the mother. Furthermore, data are now available that even transient neonatal hypothyroidism may adversely impact intellectual development in children (Dr. — personal communication to Dr. Temeck). In light of this, use of Levolet should not be recommended in pregnancy and during nursing. There is every reason to believe that other safe and effective T4-containing oral drug products not containing KI will be available to such patients. The recommendation against use in pregnant or nursing women should be addressed — The recommended Pregnancy Category is — The recommendation against use in pregnant women is based upon data in humans using KI which suggest a potential risk to the fetus. Despite this, thyroid hormone is essential to the life of the mother (and thus to the fetus), so if no other source of T4 is available, the benefits of Levolet will outweigh the risks to the fetus associated with its use by the mother. A reference to Warnings will be required, where the pertinent data will have to be described and language such as the following included, according to 21CFR201.57:

Levolet, because it contains iodide, may suppress fetal thyroid function when administered to a pregnant woman. (Describe data). *The risk to the fetal thyroid may be increased if the mother is otherwise taking supplemental iodine. Pregnant women requiring thyroid hormone products should use those not containing iodine if available. If this drug must be used during pregnancy (because no alternative product is available), or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.*

In patients with goiter or nodular thyroid disease, particularly the elderly or those with underlying heart disease, Levolet should be used with caution and thyroid function tests monitored to obviate hyperthyroidism and potential associated adverse cardiovascular outcomes. This information should be included in Warnings and in a potential section on Considerations in the Use of Levolet.

Patients receiving iodine for either diagnostic or therapeutic purposes should have their Levolet withheld in order to maximize uptake of radioiodine. The iodine in Levolet will block partially, at least, the uptake by the thyroid gland of the diagnostic or therapeutic radioactive iodine dose.

Recommendation

Contingent upon agreement on final labeling, including points addressed in Summary and Conclusions, above, Levolet should be approved.

David G. Orloff, M.D.
Deputy Director, DMEDP (HFD-510)
CDER/FDA

/S/ 2-21-00

Recommendation code: AP

4 pages redacted from this section of the approval package consisted of draft labeling

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

/s/

Jean Temeck
7/2/01 02:19:56 PM
MEDICAL OFFICER

David Orloff
7/2/01 08:50:27 PM
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APPEARS THIS WAY ON ORIGINAL

NDA: 21,137 Drug: Levolet (Levothyroxine sodium: T4) Sponsor: Vintage Pharm.
Date: 3/7/2000

Addendum to Medical Officer's Review Dated 2/11/2000:

Background:

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

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 receiving large doses of T4 who have low TSH concentrations may have increased heart rates, arrhythmias and cardiac contractility as well as left ventricular hypertrophy. Elderly patients have an increased risk of atrial fibrillation.

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 remainder of this review will be organized as follows:

15. Bibliography: pages 32-38.

1. REGULATION OF THYROID HORMONE SECRETION:

TRH (thyrotropin-releasing hormone), 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.

2.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.

3. 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.

3.A. Effects of thyroid hormones on metabolism:

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

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

3.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.

3.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.

3.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.

4. PHARMACOKINETICS:

4.A. Absorption:

Absorption of orally administered T4 from the GI tract ranges from [illegible]% 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.

4.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.

4.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.

4.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.

4.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.

5. 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.

6. CLINICAL SIGNS AND SYMPTOMS:

6.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.

6.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 retration;

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.

7. LABORATORY EVALUATION:

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

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

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

8. 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.

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

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

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

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

- Adults with hypothyroidism require 1.7 ug/kg/day for full T4 replacement.

- Therapy is usually initiated in patients under the age of 50 years with full replacement.
- For patients older than 50 years or younger patients with a history of cardiac disease, an initial starting dose of 25-50 ug levothyroxine daily is recommended, with clinical and biochemical evaluations at 6-8 week intervals until the serum TSH level is normalized.
- Once the serum TSH level has normalized, visits every 6-12 months is sufficient, depending on the clinical situation. A physical examination should be performed annually and a serum TSH measured at least annually. For patients who have recently started receiving levothyroxine but their serum TSH has normalized, or who have had their dosage, type or brand of thyroid preparation changed, the serum TSH concentration should be measured after 8-12 weeks.
- Some individuals older than 50 years, such as those recently treated for hyperthyroidism or those known to have had hypothyroidism for only a short time (such as a few months), may be treated with full replacement doses of levothyroxine.
- Pregnancy may increase levothyroxine requirements in hypothyroid patients. Serum TSH should be monitored during each trimester and appropriate adjustments made in levothyroxine dosage. The levothyroxine dosage should return to the prepregnancy dose immediately after delivery, and a serum TSH level should be obtained 6-8 weeks postpartum.
- If symptoms of palpitations, tremor, difficulty in concentrating, or chest pain are confirmed to be secondary to hyperthyroidism, levothyroxine therapy should be withheld for one week and restarted at a lower dose.
- Since levothyroxine overreplacement has been associated with reduced bone mineral content, particularly in postmenopausal women, it is recommended that these patients have their dose reduced until the TSH concentration is normalized, unless TSH suppression is the objective, as in patients with a history of well-differentiated thyroid cancer.
- Levothyroxine dosing should be spaced at least 4 hours apart from drugs that are known to interfere levothyroxine absorption from the gut, such as cholestyramine, ferrous sulfate, sucralfate and aluminum hydroxide antacids.
- Drugs that accelerate levothyroxine metabolism such as the anticonvulsants, phenytoin and carbamazepine and the antituberculous agent rifampin, may necessitate higher levothyroxine doses.

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

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

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

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

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

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

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

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

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

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.

Pregnant women and obese patients may require higher than average T4 replacement doses.

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

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

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

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

8.B. Levothyroxine dose requirements in pediatric patients:

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

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

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

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

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

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

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

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

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

a. The optimal maintenance dose for the treatment of acquired juvenile hypothyroidism is the dose that normalizes the serum TSH concentration and maintains the serum T4 in the midrange or upper range of normal for age, and that normalizes growth.
b. Excessive doage 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.

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.

9. 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.

10. SUMMARY OF SAFETY DATA:

10.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.

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

10.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.

10.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 and that this risk was significant only for patients <65 years old.

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 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.

The most frequently encountered severe complications of the thyrotoxic condition are tachyarrhythmias, throboembolism 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).

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

a. On Bone Mineral Density:

Ross et al (Amer J Med 82:167-170, 1987) found a 9% decrement in forearm cortical bone density in 12/28 premenopausal patients who had been receiving levothyroxine therapy for $\geq$ 10 years. However, in the majority of these patients, therapy was suppressive as judged by a high FT4I and a flat or subnormal TRH stimulation test.

Paul et al (JAMA 259:3137-3141, 1988) examined a group of 31 treated premenopausal women and found that, compared with control subjects, bone density was 12.8% lower at the femoral neck and 10.1% lower at the trochanter. The mean FT4I was at the upper limit of normal and significantly higher than in the control group, consistent with mild overreplacement.

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 and trochanter sites, Ward's triangle, arms and pelvis (Kung et al, JAMA 265:2688-2691, 1991).

Stoll et al (Ann Int Med 113:265-9, 1990) reported accelerated bone loss in hypothyroid women overtreated with levothyroxine.

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 postmenopausal women who did not have a history of hyperthyroidism, did not have decreased mineral density of the femoral neck, Ward's triangle and trochanter, when the patients were administered levothyroxine for at least 5 years. Franklyn et al (Lancet 340:9-13, 1992) also did not find a change in bone mineral density in pre- and postmenopausal women on chronic thyroid hormone replacement therapy.

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.

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.

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

9. **DRUG-DRUG INTERACTIONS:**

11.A. Drugs that decrease TSH secretion:

Dopamine
Glucocorticoids
Octreotide

11.B. Drugs that alter thyroid hormone secretion:

Decrease secretion:
- Lithium
- Iodide
- Amiodarone
- Aminoglutethimide

Increase secretion:
- Iodide
- Amiodarone

11.C. Drugs that decrease T4 absorption:

- Colestipol
- Cholestyramine
- Colestipol/Niacin
- Aluminum hydroxide
- Ferrous sulfate
- Sucralfate

11.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

11.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

11.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.

11.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.

12. 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.

13. DRUG 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.

14. LEVOTHYROXINE CLASS LABELING:

My comments refer to the attached draft class labeling dated 1/13/2000:

C

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11 pages redacted from this section of the approval package consisted of draft labeling

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). However, in children with long-standing or severe hypothyroidism, an initial dose of 25 ug levothyroxine/day is recommended with increments of 25 ug 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, breast milk or non-soybean formula. This suspension can be administered by spoon or dropper. DO NOT STORE THE SUSPENSION. The crushed tablet may also be sprinkled over a small amount of food (e.g. applesauce). Foods which decrease absorption of levothyroxine such as fiber, soybean or iron, should not be used for administering levothyroxine.

The following are levothyroxine dosing guidelines for Pediatric Hypothyroidism:

AGE	Daily Dose Per Kg Body Weight[a]
0-3 months	10-15 /kg/day
3-6 months	8-10 /kg/day
6-12 months	6-8 /kg/day
1-5 years	5-6 /kg/day
6-12 years	4-5 /kg/day
>12 years	2-3 /kg/day
Growth and puberty complete	1.7 /kg/day

[a] The dose should be adjusted based on clinical response and laboratory parameters (see LABORATORY TESTS: DIAGNOSIS AND MONITORING).

/S/

Jean Temeck, M.D.

Bibliography is appended

cc. NDA Arch 21, 137
NDA Div file
HFD-510: Dr. Steigerwalt, Dr. Johnson and Mr. McCort

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