

Levothyroxine Sodium for Injection

Thyroid Hormone

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Injection (intravenous or intramuscular)	Lyophilized Powder/ 500 µg/vial	Mannitol, tribasic sodium phosphate anhydrous, and sodium hydroxide

INDICATIONS AND CLINICAL USE

Levothyroxine Sodium for Injection is indicated for:

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

Levothyroxine sodium by the intravenous route can be substituted for the oral dosage form when rapid repletion is required; or by the intravenous or intramuscular route when oral administration is precluded.

Geriatrics: No data is available.

Pediatrics: No data is available.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.
- Patients with untreated subclinical (suppressed serum TSH level with normal T₃ and T₄ levels) or overt thyrotoxicosis of any etiology and in patients with acute myocardial infarction.
- Patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see **WARNINGS AND PRECAUTIONS, Immune, Autoimmune Polyglandular Syndrome**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Thyroid hormones, including levothyroxine, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss. 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.

General

Levothyroxine has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or undertreatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Many drugs interact with levothyroxine sodium, necessitating adjustments in dosing to maintain therapeutic response (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Cardiovascular

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. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatric Use** and **DOSAGE AND ADMINISTRATION, Administration**). If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced. 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. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Endocrine and Metabolism

Hypothalamic/Pituitary Hormone Deficiencies

In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated (see **WARNINGS AND PRECAUTIONS, Immune, Autoimmune Polyglandular Syndrome**) for adrenal insufficiency.

Bone Mineral Density

In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in postmenopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorus, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Immune

Autoimmune Polyglandular Syndrome

Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with levothyroxine sodium. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with levothyroxine (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Sexual Function/Reproduction

Levothyroxine sodium should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism. Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of levothyroxine. The synthetic T₄ in levothyroxine 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 for appropriate clinical indications should be titrated to the lowest effective replacement dose.

Special Populations

Pregnant Women

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. Levothyroxine should not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be promptly treated.

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. 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 should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of levothyroxine. 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 extent as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent *in utero* hypothyroidism.

Nursing Women

Although thyroid hormones are excreted only minimally in human milk, caution should be exercised when levothyroxine is administered to a nursing woman. However, adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

Pediatrics

The goal of treatment in pediatric patients with hypothyroidism is to achieve and maintain normal intellectual and physical growth and development.

The initial dose of levothyroxine varies with age and body weight. Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics**).

The presence of concomitant medical conditions should be considered in certain clinical circumstances and, if present, appropriately treated (see **WARNINGS AND PRECAUTIONS, General**).

Congenital Hypothyroidism (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics**; and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**)

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.

Rapid restoration of normal serum T₄ concentrations is essential for preventing the adverse effects of congenital 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.

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

The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. 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.

Acquired Hypothyroidism in Pediatric Patients

The patient should be monitored closely to avoid undertreatment and overtreatment. 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.

Treated children may manifest a 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.

Geriatric Use

Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **DOSAGE AND ADMINISTRATION, Administration**).

Monitoring and Laboratory Tests

General

The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay (second generation assay sensitivity ≤ 0.1 mIU/L or third generation assay sensitivity ≤ 0.01 mIU/L) and measurement of free-T₄.

The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. The 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 the use of concomitant medications (see **DRUG INTERACTIONS, Drug-Drug Interactions and Drug-Laboratory Interactions**). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of levothyroxine may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T₄ potency of the drug product.

Adults

In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels (using a sensitive assay) alone may be used to monitor therapy. The frequency of TSH monitoring during levothyroxine dose titration depends on the clinical situation but it is generally recommended at 6 - 8 week intervals until normalization. For patients who have recently initiated levothyroxine therapy and whose serum TSH has normalized, or in patients who have had their dosage of levothyroxine changed, the serum TSH concentration should be measured after 8 - 12 weeks. When the optimum replacement dose has been attained, clinical (physical examination) 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. It is recommended that a physical examination and a serum TSH measurement be performed at least annually in patients receiving levothyroxine.

Pediatrics

In patients with congenital hypothyroidism, the adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free-T₄. During the first three years of life, the serum total- or free-T₄ should be maintained at all times in the upper half of the normal range. 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. TSH may not normalize 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 of the serum

TSH to decrease below 20 mIU/L within 4 weeks should alert the physician to the possibility that the child is not receiving adequate therapy.

The recommended frequency of monitoring of TSH and total- or free-T₄ in children 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; and every 3 - 12 months thereafter until growth is completed. More frequent intervals of monitoring may be necessary if abnormal values are obtained. It is recommended that TSH and T₄ levels, and a physical examination, if indicated, 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 (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Secondary (Pituitary) and Tertiary (Hypothalamic) Hypothyroidism

Adequacy of therapy should be assessed by measuring serum free-T₄ levels, which should be maintained in the upper half of the normal range in these patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage (see **WARNINGS AND PRECAUTIONS, General** and **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;

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

Respiratory: dyspnea;

Gastrointestinal: diarrhea, vomiting, abdominal cramps and elevations in liver function tests;

Dermatologic: hair loss, flushing;

Endocrine: decreased bone mineral density;

Reproductive: menstrual irregularities, impaired fertility.

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

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

Inadequate levothyroxine dosage will produce or fail to ameliorate the signs and symptoms of hypothyroidism.

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

DRUG INTERACTIONS

Overview

Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to levothyroxine. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and actions of other drugs. A listing of drug-thyroidal axis interactions is contained in **Table 1**.

Oral Anticoagulants

Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant 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 **Table 1**).

Digitalis Glycosides

The therapeutic effects of digitalis glycosides may be reduced by levothyroxine. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see **Table 1**).

Drug-Drug Interactions

The list of drug-thyroidal axis interactions in **Table 1** may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources (e.g., package inserts of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

Table 1: Established or Potential Drug-Drug Interactions			
Drug or Drug Class	Ref	Effect	Clinical Comment
Drugs that may reduce TSH secretion – the reduction is not sustained; therefore, hypothyroidism does not occur			
Dopamine/ Dopamine Agonists Glucocorticoids Octreotide	CT	Use of these agents may result in a transient reduction in TSH secretion.	Reduction 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			
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism			
Amino-glutethimide Amiodarone Iodide (including iodine-containing radiographic contrast agents) Lithium Methimazole Propylthiouracil (PTU) Sulfonamides Tolbutamide	CT	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. 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.	The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Graves' disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism			
Amiodarone Iodide (including iodine-containing radiographic contrast agents)	CT	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Graves' 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.
Drugs that may alter T_4 and T_3 serum transport – but FT_4 concentration remains normal; therefore, the patient remains euthyroid			
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin/Mehtadone 5-Fluorouracil Mitotane Tamoxifen	CT	Increase serum TBG concentration	N/A
Androgens/ Anabolic Steroids Asparaginase Glucocorticoids Slow-release Nicotinic Acid	CT	Decrease serum TBG concentration	N/A
Drugs that may cause protein-binding site displacement			
Furosemide ($> 80 \text{ mg i.v.}$) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs – Fenamates – Phenylbutazone Salicylates ($> 2 \text{ g}/\text{day}$)	CT	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%.
<i>(continued)</i>			

Table 1: Established or Potential Drug-Drug Interactions <i>(continued)</i>			
Drug or Drug Class	Ref	Effect	Clinical Comment
Drugs that may alter T_4 and T_3 metabolism			
Drugs that may increase hepatic metabolism, which may result in hypothyroidism			
Carbamazepine Hydantoins Phenobarbital Rifampin	CT	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine 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.	N/A
Drugs that may decrease T_4 5'-deiodinase activity			
Amiodarone Beta-adrenergic antagonists – (e.g., Propranolol $> 160 \text{ mg}/\text{day}$) Glucocorticoids – (e.g., Dexamethasone $\geq 4 \text{ mg}/\text{day}$) Propylthiouracil (PTU)	CT	Administration of these enzyme inhibitors decreases 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 ($> 160 \text{ mg}/\text{day}$), 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	CT	Thyroid 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)	CT	Concurrent use of tri/tetracyclic 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	CT	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.
<i>(continued)</i>			

Drug or Drug Class	Ref	Effect	Clinical Comment
Miscellaneous (continued)			
Cytokines		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. 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.	Patients who have anti-thyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment.
Growth Hormones – Somatrem – Somatropin	CT	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure.	Untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	CT	Concurrent use may produce marked hypertension and tachycardia.	Cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators – (e.g., Theophylline)	CT	Decreased theophylline clearance may occur in hypothyroid patients.	Clearance returns to normal when the euthyroid state is achieved.
Radiographic Agents	CT	Thyroid hormones may reduce the uptake of ^{123}I , ^{131}I , and $^{99\text{m}}\text{Tc}$.	N/A
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 Nitroprusside Para-amino-salicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	CT	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.	N/A

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Changes in TBG concentration must be considered when interpreting T_4 and T_3 values, which necessitate measurement and evaluation of unbound (free) hormone and/or determination of the free- T_4 index (FT $_4$). 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 (see also Table 1). Familial hyper- or hypothyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state.

The dose of levothyroxine that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see **WARNINGS AND PRECAUTIONS, General**). Dosing must be individualized and adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, General**).

Administration

Levothyroxine sodium by the intravenous route can be substituted for the oral dosage form when rapid repletion is required; or by the intravenous or intramuscular route when oral administration is precluded.

Administration of Levothyroxine Sodium for Injection by the subcutaneous route is not recommended as studies have shown that the influx of T_4 from the subcutaneous site is very slow, and depends on many factors such as volume of injection, the anatomic site of injection, ambient temperature, and presence of venospasm.

Due to the long half-life of levothyroxine, the peak therapeutic effect at a given dose of levothyroxine sodium may not be attained for 4-6 weeks.

Caution should be exercised when administering levothyroxine to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Reconstitution

Reconstitute the lyophilized levothyroxine sodium by aseptically adding 5 mL of 0.9% Sodium Chloride Injection, USP only. **Do not use Bacteriostatic Sodium Chloride Injection, USP, as the bacteriostatic agent may interfere with complete reconstitution.** Shake vial to ensure complete mixing. Use immediately after reconstitution. Do not add to other intravenous fluids. Single-dose vial. Discard any unused portion.

As with all parenteral products, intravenous admixtures should be inspected for clarity of solutions, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Recommended Dose and Dosage Adjustment

The initial parenteral dosage should be approximately one-half the previously established oral dosage of levothyroxine sodium tablets.

Specific Patient Populations

A) Hypothyroidism in Adults and in Children in Whom Growth and Puberty are Complete (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Adults**)

Clinical and laboratory evaluations should generally be performed at 6 to 8 week intervals (2 to 4 weeks in severely hypothyroid patients), and the dosage adjusted, if necessary, until the serum TSH concentration is normalized and signs and symptoms resolve (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Adults**). If cardiac symptoms develop or worsen, the cardiac disease should be evaluated and the dose of levothyroxine reduced (see **WARNINGS AND PRECAUTIONS, Cardiovascular**). Rarely, worsening angina or other signs of cardiac ischemia may prevent achieving a TSH in the normal range.

In the elderly, the full replacement dose may be altered by decreases in T_4 metabolism.

B) Pediatric Dosage – Congenital or Acquired Hypothyroidism (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics**)

Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development.

Undertreatment and overtreatment should be avoided (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics**).

The aim of therapy for congenital hypothyroidism is to achieve and maintain normal growth and development. During the first three years of life, serum T_4 concentrations should be maintained in the upper half of the normal range and, if possible, serum TSH should be normalized. (See **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics**.)

C) Pregnancy

Pregnancy may increase levothyroxine requirements (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

D) Myxedema Coma

Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral thyroid hormone drug products are not recommended to treat this condition. Thyroid hormone drug products formulated for intravenous administration should be administered. A bolus dose of levothyroxine sodium is given immediately to replete the peripheral pool of T_4 , usually 300 to 500 μg . Although such a dose is usually well tolerated even in the elderly, the rapid intravenous administration of large doses of levothyroxine sodium to patients with cardiovascular disease is clearly not without risks. Under such circumstances, intravenous therapy should not be undertaken without weighing the alternate risks of myxedema coma and the cardiovascular disease. Clinical judgement in this situation may dictate smaller intravenous doses of levothyroxine sodium. The initial dose is followed by daily intravenous doses of 75 to 100 μg until the patient is stable and oral administration is feasible. Normal T_4 levels are usually achieved in 24 hours, followed by progressive increases in T_3 . Improvement in cardiac output, blood pressure, temperature, and mental status generally occur within 24 hours, with improvement in many manifestations of hypothyroidism in 4 to 7 days.

OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism (see **WARNINGS AND PRECAUTIONS, General** and **ADVERSE REACTIONS, Adverse Drug Reaction**).

Overview) In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures have occurred in a child ingesting approximately 18 mg of levothyroxine. Symptoms may not necessarily be evident or may not appear until several days after ingestion of levothyroxine sodium.

Levothyroxine sodium should be reduced in dose or temporarily discontinued if signs or symptoms of overdosage occur.

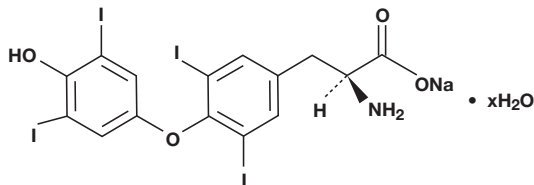
Acute Massive Overdosage

This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. Central and peripheral increased sympathetic activity may be treated by administering β -receptor antagonists, e.g., propranolol, provided that there are no medical contraindications to their use. Provide respiratory support as needed; control congestive heart failure and arrhythmia; control fever, hypoglycemia, and fluid loss as necessary. Large doses of antithyroid drugs (e.g., methimazole or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones. Glucocorticoids may be given to inhibit the conversion of T_4 to T_3 . Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Because T_4 is highly protein bound, very little drug will be removed by dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Levothyroxine Sodium for Injection contains synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T_4 is identical to that produced in the human thyroid gland. Levothyroxine (T_4) sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$, molecular weight of 798.85 g/mol (anhydrous), and structural formula as shown:



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 hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), by the thyroid gland. Circulating serum T_3 and T_4 levels exert a feedback effect on both TRH and TSH secretions. When serum T_3 and T_4 levels increase, TRH and TSH secretions decrease. When thyroid hormone levels decrease, TRH and TSH secretions 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. T_3 and T_4 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 regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development.

The physiological actions of thyroid hormones are produced predominantly by T_3 , the majority of which (approximately 80%) is derived from T_4 by deiodination in peripheral tissues.

Levothyroxine, at doses individualized according to patient response, is effective as replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.

Pharmacokinetics

Distribution: Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding pre-albumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to T_3 . Protein-bound thyroid 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 INTERACTIONS, Drug-Drug Interactions** and **Drug-Laboratory Interactions**). Thyroid hormones do not readily cross the placental barrier (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

Metabolism: T_4 is slowly eliminated (see **Table 2**). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3 , with T_4 deiodination also occurring at a number

of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (rT_3). T_3 and rT_3 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 they undergo enterohepatic recirculation.

Excretion: 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 T_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%) ²
Levothyroxine (T_4)	10 - 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

STORAGE AND STABILITY

Store at controlled room temperature between 15 and 30°C (59 - 86°F), protected from light.

Single-dose vial. Use immediately after reconstitution. Discard any unused portion. Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Levothyroxine Sodium for Injection contains synthetic crystalline Levothyroxine Sodium, USP and the following inactive ingredients: mannitol, tribasic sodium phosphate anhydrous and sodium hydroxide.

Availability of Dosage Forms

Levothyroxine Sodium for Injection is a sterile lyophilized powder for reconstitution. It is supplied in 10 mL single-dose vials containing 500 μ g of Levothyroxine Sodium, USP.

C24810 500 μ g levothyroxine sodium, USP in 10 mL vials packaged individually.

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