PRODUCT MONOGRAPH

Pr LEVOTHYROXINE SODIUM FOR INJECTION

Levothyroxine Sodium for Injection

Lyophilized Powder

200 mcg/vial and 500 mcg/vial

Thyroid Hormone

Imported by: Laboratoire Riva Inc.
Distributed by: **AVIR Pharma Inc.**

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Injection (intravenous or intramuscular)	Lyophilized powder 200 mcg/vial, 500 mcg/vial	Mannitol, dibasic sodium phosphate heptahydrate, and sodium hydroxide.

INDICATIONS AND CLINICAL USE

LEVOTHYROXINE SODIUM FOR INJECTION (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.

Pediatrics: LEVOTHYROXINE SODIUM FOR INJECTION is approved for use in the pediatric population. However, dosing and monitoring considerations apply (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Pediatric Dosage***).

Geriatrics: LEVOTHYROXINE SODIUM FOR INJECTION is approved for use in the geriatric population. However, dosing precautions apply (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Geriatric Dosage***).

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 T_3 and T_4 levels) or overt thyrotoxicosis of any etiology.
- Patients with acute myocardial infarction, acute myocarditis, or acute pancarditis.
- 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**).

- Combination therapy of LEVOTHYROXINE SODIUM FOR INJECTION and an antithyroid agent for hyperthyroidism during pregnancy (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

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**).

Before starting therapy with thyroid hormones or before performing a thyroid suppression test, the following diseases or medical conditions must be excluded or treated: coronary failure, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency, or adrenal insufficiency. Thyroid autonomy should also be excluded or treated before starting therapy with thyroid hormones.

The etiology of secondary hypothyroidism must be determined before thyroid hormone replacement therapy is given. If necessary, replacement treatment of a compensated adrenal insufficiency must be commenced.

LEVOTHYROXINE SODIUM FOR INJECTION therapy for patients with previously undiagnosed endocrine disorders, including adrenal insufficiency, hypopituitarism, and diabetes insipidus, may worsen symptoms of these endocrinopathies.

Seizures have been reported rarely in association with the initiation of levothyroxine sodium therapy, and may be related to the effect of thyroid hormone on seizure threshold.

Carcinogenesis and Mutagenesis

Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic T_4 is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid hormone therapy and breast cancer has not been confirmed and patients receiving levothyroxine for established indications should not discontinue therapy.

Cardiovascular

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. If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced. 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. Hence, frequent checks of thyroid hormone parameters must be performed in these cases.

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, Recommended Dose and Dosage Adjustment, *Geriatric Dosage***).

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 for adrenal insufficiency (see **WARNINGS AND PRECAUTIONS, Immune, Autoimmune Polyglandular Syndrome**).

Levothyroxine sodium is not recommended in hyperthyroid metabolic states. An exception is the concomitant supplementation during anti-thyroid drug treatment of hyperthyroidism.

Bone Mineral Density: In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine sodium have to be avoided and close monitoring of the thyroid function is recommended. 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**).

Hematologic

T_4 enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both levothyroxine and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Psychiatric

When initiating levothyroxine therapy in patients at risk of psychotic disorders, it is recommended to start at a low levothyroxine dose and to slowly increase the dosage at the beginning of the therapy. Monitoring of the patient is advised. If signs of psychotic disorders occur, adjustment of the dose of levothyroxine should be considered.

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 effects of levothyroxine on fertility.

Special Populations

Pregnant Women: Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. 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 T_4 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.

Combination therapy of levothyroxine and an antithyroid agent for hyperthyroidism is contraindicated during pregnancy (see CONTRAINDICATIONS). Such combination would require higher doses of anti-thyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

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

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

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

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.

Congenital Hypothyroidism

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 T_4 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.

Acquired Hypothyroidism in Pediatric Patients

If transient hypothyroidism is suspected, hypothyroidism permanence may be assessed after the child reaches 3 years of age. Levothyroxine therapy may be interrupted for 30 days and serum T_4 and TSH measured. Low T_4 and elevated TSH confirm permanent hypothyroidism; therapy should be re-instituted. If T_4 and TSH remain in the normal range, a presumptive diagnosis of transient hypothyroidism can be made. In this instance, continued clinical monitoring and periodic thyroid function test re-evaluation may be warranted.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, an alternate approach is to reduce the replacement dose of levothyroxine by half during the 30-day trial period. If, after 30 days, the serum TSH is elevated above 20 mU/L, the diagnosis of permanent hypothyroidism is confirmed, and full replacement therapy should be resumed. However, if the serum TSH has not risen to greater than 20 mU/L, levothyroxine treatment should be discontinued for another 30-day trial period followed by repeat serum T_4 and TSH testing.

Geriatrics Use: Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose. Atrial fibrillation is a common side effect associated with levothyroxine treatment in the elderly (see **WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Geriatric Dosage***).

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-T_4.

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 T_4 potency of the drug product.

Where thyroid autonomy is suspected, a Thyroid Releasing Hormone (TRH) test or a suppression scintigram is recommended before initiation of treatment.

Adequacy of levothyroxine sodium therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring free T_4, which should be maintained in the upper half of the normal range. Measurement of TSH is not a reliable indicator of response to therapy for this condition.

Adults: In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels 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

Pediatrics:

Congenital Hypothyroidism: Adequacy of replacement therapy should be assessed by measuring both serum TSH and total- or free-T_4. During the first three years of life, the serum total- or free-T_4 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 T_4 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-T_4 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 T_4 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-T_4 levels, which should be maintained in the upper half of the normal range in these patients. Measurement of TSH is not a reliable indicator of response to therapy for this condition

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage.

Nervous system: headache, hyperactivity, nervousness, restlessness, anxiety, irritability, emotional lability, insomnia, pseudotumour cerebri, seizures;

Musculoskeletal: tremors, muscle weakness, cramps, slipped capital femoral epiphysis, craniosynostosis (with reduced adult height);

Cardiovascular: palpitations, tachycardia, cardiac arrhythmias (e.g., atrial fibrillation and extrasystoles), increased pulse and blood pressure, heart failure, angina pectoris, 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;

Immune: hypersensitivity reactions (urticaria, pruritus, skin rash, flushing, angioedema, various abdominal pain, nausea, vomiting and diarrhea, fever, arthralgia, serum sickness and wheezing).

Other: fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating, exophthalmic goiter, pseudotumor cerebri (in children).

Clinical signs of hyperthyroidism may occur in case of overdose, if the individual tolerance limit for levothyroxine sodium is exceeded, or if the dose is increased too fast at the start of treatment. In such cases the daily dose has to be reduced or the medication withdrawn for several days. Therapy may carefully be resumed once the adverse reactions have disappeared (see **OVERDOSAGE**).

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**.

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.

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 (≥ 1 mcg/kg/min); Glucocorticoids (hydrocortisone ≥ 100 mg/day or equivalent); Octreotide (> 100 mcg/day).
Drugs that alter thyroid hormone secretion			
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism			
Aminoglutethimide 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.

Drug or Drug Class	Ref	Effect	Clinical comment
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism			
Amiodarone Iodide (including iodine-containing radiographic contrast agents) Sertraline Chloroquinone Proguanil	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). Sertraline, Chloroquinone / Proguanil decrease the efficacy of levothyroxine sodium and increase the serum TSH level.	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/Methadone 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 mg i.v.) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs - Fenamates - Phenylbutazone Salicylates (> 2 g/day) Dicumarol Furosemide in high doses (250mg) Clofibrate	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%.

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 (e.g. Phenytoin) Barbiturates (e.g. Phenobarbital) Rifampin	CT	Stimulation of hepatic microsomal drug-metabolizing enzyme activity by drugs like phenytoin may cause increased hepatic degradation/ clearance of levothyroxine, resulting in increased levothyroxine requirements. On the other hand, phenytoin may influence the effect of levothyroxine sodium by displacing levothyroxine sodium from plasma proteins resulting in an elevated fT_4 and fT_3 fraction. Carbamazepine reduces 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			
Iodine containing contrast media Amiodarone Beta-adrenergic antagonists/ beta sympatholytics - (e.g., Propranolol > 160 mg/day) Glucocorticoids - (e.g., Dexamethasone ≥ 4 mg/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 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. Due to its high iodine content amiodarone can trigger hyperthyroidism as well as hypothyroidism.	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). In levothyroxine patients with concomitant use of Amiodarone, particular caution is advised in the case of nodular goiter with possibly unrecognised autonomy.
Miscellaneous			
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	CT	Levothyroxine sodium may intensify the effect of anticoagulants by displacing them from plasma protein bounds which may increase the risk of haemorrhage, e.g. CNS or gastrointestinal bleeding, especially in elderly patients. 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.	Check the coagulation parameters regularly at the start of and during concomitant therapy. Prothrombin time can be carefully monitored in patients taking levothyroxine and if necessary, the anticoagulant dose has to be altered.

Drug or Drug Class	Ref	Effect	Clinical comment
Antidepressants - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline, chloroquine/proguanil)	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. Sertraline, chloroquine/proguanil: these substances decrease the efficacy of levothyroxine sodium and increase the serum TSH level.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidediones - Insulin	CT	Levothyroxine sodium may reduce the effect of anti-diabetics. If necessary, the anti-diabetic dose has to be adjusted.	It is necessary to check blood glucose levels frequently at the start of thyroid hormone therapy or when thyroid hormone therapy is changed or discontinued.
Digitalis Glycosides	CT	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state necessitating an increase in the dose of digitalis glycosides.	Therapeutic effect of digitalis glycosides may be reduced by levothyroxine sodium.
Cytokines	CT	Therapy with interferon-α has been associated with the development of antithyroid microsomal antibodies in 20% of patients, and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients.	Interferon-β and -γ have not been reported to cause thyroid dysfunction.
Growth Hormones - Somatrem - Somatropin	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 ^{99m}Tc.	N/A
Estrogens	CT	Women using estrogen-containing contraceptives or postmenopausal women under hormone -replacement therapy may have an increased need for levothyroxine sodium.	N/A
Protease inhibitors	CT	Protease inhibitors (e.g. ritonavir, indinavir, lopinavir) may influence the effect of levothyroxine sodium.	Close monitoring of thyroid hormone parameters is recommended. If necessary, the levothyroxine sodium dose has to be adjusted.

Drug or Drug Class	Ref	Effect	Clinical comment
Proton Pump Inhibitors	T	Plasma concentration of levothyroxine (thyroxine) is possibly reduced by Proton Pump Inhibitors.	Monitoring of TSH plasma level is recommended.
Sympathomimetics	CT	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.
Tyrosine-kinase inhibitors	CT	Tyrosine-kinase inhibitors (e.g. imatinib, sunitinib) may decrease the efficacy of levothyroxine sodium.	Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the levothyroxine sodium dose has to be adjusted.
Orlistat	N/A	Hypothyroidism and / or reduced control of hypothyroidism may occur when orlistat and levothyroxine are co-administered	Patients taking orlistat with levothyroxine should take the drugs at separate times. Thyroid hormone levels should be monitored more closely as the dose may need to be adjusted
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate 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

A number of drugs or moieties are known to alter serum levels of TSH, T_4 and T_3 and may thereby influence the interpretation of laboratory tests of thyroid function (see **Table 1).**

Changes in Thyroid-Binding Globule (TBG) concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free-T_4 index (FT_4I). 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 glucocorticoid therapy (see **Table 1**).

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. 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**).

Recommended Dose and Dosage Adjustment

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

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**).

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.

Pediatric Dosage – Congenital or Acquired Hypothyroidism

The aim of therapy is to achieve and maintain normal growth and development. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical 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. Undertreatment and overtreatment should be avoided. (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics.**).

Geriatric Dosage

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).

Pregnancy

Treatment with thyroid hormones is given consistently during pregnancy. Pregnancy may increase levothyroxine sodium requirements (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

There is no evidence of drug-induced teratogenicity and/or feto-toxicity in humans at the recommended therapeutic dose level. Excessively high dose levels of levothyroxine sodium during pregnancy may have a negative effect on fetal and postnatal development.

Lactation

Adequate replacement doses of levothyroxine are generally needed to maintain normal lactation. Treatment with thyroid hormones is given consistently during lactation. Levothyroxine sodium is secreted into breast milk during lactation but the concentrations achieved at the recommended therapeutic dose level are not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant.

Myxedema Coma

Myxedema coma represents the extreme expression of severe hypothyroidism and is considered a life-threatening medical emergency. It is characterized by hypothermia, hypotension, hypoventilation, hyponatremia, and bradycardia. In addition to restoration of normal thyroid hormone levels, therapy should be directed at the correction of electrolyte disturbances and possible infection. Because the mortality rate of patients with untreated myxedema coma is high, treatment must be started immediately, and should include appropriate supportive therapy and corticosteroids to prevent adrenal insufficiency. Possible precipitating factors should also be identified and treated.

A bolus dose of levothyroxine sodium is given immediately to replete the peripheral pool of T_4, usually 300 to 500 mcg. 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 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 judgment in this situation may dictate smaller intravenous doses of levothyroxine sodium. The initial dose is followed by daily intravenous doses of 75 to 100 mcg 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.

Administration

LEVOTHYROXINE SODIUM FOR INJECTION (Levothyroxine Sodium for Injection) can be used intravenously in place of the oral dosage form when rapid repletion is required. It can also be used intravenously or intramuscularly 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.** The resultant solution will have a final concentration of approximately 40 mcg/mL and 100 mcg/mL for the 200 mcg and 500 mcg vials, respectively. Shake vial to ensure complete mixing. Use immediately after reconstitution. Do not add to other intravenous fluids.

LEVOTHYROXINE SODIUM FOR INJECTION comes in a single-dose vial, and any unused portion should be discarded.

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

Missed Dose

The missed dose should be administered as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next regularly scheduled dose should be administered. Doses should not be doubled.

OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism (see **ADVERSE REACTIONS, Adverse Drug Reaction Overview**). Overdose may cause symptoms of a significant increase in the metabolic rate. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Levothyroxine overdose may also lead to symptoms of acute psychosis, especially in patients at risk of psychotic disorders. Symptoms may appear several days after the overdose of levothyroxine sodium. Several cases of sudden cardiac death have also been reported in patients with many years of levothyroxine sodium abuse.

An elevated T_3 level is a reliable indicator of overdose, more so than elevated T_4 or f T_4 levels.

Depending on the extent of the overdose it is recommended that treatment is interrupted and that thyroid hormone monitored.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Acute Massive Overdosage: This may be a life-threatening emergency; therefore, symptomatic and supportive therapy should be instituted immediately. Beta-sympathomimetic effects or central and peripheral increased sympathetic activity such as tachycardia, anxiety, agitation or hyperkinesia may be treated by administering betablockers, 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. Due to its high protein binding, levothyroxine sodium cannot be eliminated via hemodialysis or hemoperfusion.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

LEVOTHYROXINE SODIUM FOR INJECTION (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.

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.

Table 2 - Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{½}$ (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, protected from light.

Single-dose vial. Use immediately after reconstitution. The reconstituted drug product is stable for a period of 4 hours at 25°C. 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 (Levothyroxine Sodium for Injection) contains Levothyroxine Sodium, USP and the following inactive ingredients: mannitol, dibasic sodium phosphate heptahydrate and sodium hydroxide. LEVOTHYROXINE SODIUM FOR INJECTION is latex-free.

Availability of Dosage Forms

LEVOTHYROXINE SODIUM FOR INJECTION is a sterile lyophilized powder for reconstitution. It is supplied in 10 mL single-dose vials:

200 mcg levothyroxine sodium, USP in 10 mL vials packaged individually.
500 mcg levothyroxine sodium, USP in 10 mL vials packaged individually.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Sodium Levothyroxine is a physiologically active material being the levo-isomer of thyroxine.

Proper name: Sodium Levothyroxine (L-T_4, Na)

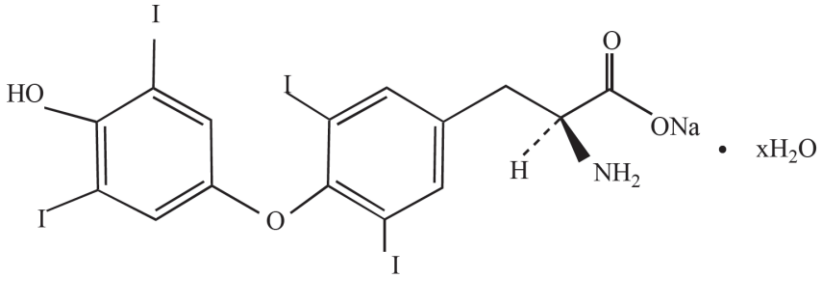
Chemical name: USP: (1) L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt

(2) Monosodium L-thyroxine hydrate

EP: sodium(2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3, 5-dioodophenyl] propanoate

Molecular formula and molecular mass: $C_{15}H_{10}I_4NNaO_4 \bullet xH_2O$
798.85 g/mol (anhydrous)

Structural formula:



Physicochemical properties: Off-white to slightly brownish-yellow powder or fine, faintly coloured crystalline powder

Solubility:

Very slightly soluble in water
Slightly soluble in ethanol
Soluble in alkali hydroxide solutions

Solvent	g/100 mL
H_2O	0.14
95% ethanol	0.3, 0.4
alkali hydroxides	soluble
chloroform	almost insoluble
ethyl ether	almost insoluble
pH 7.4 buffer	0.022 - 0.044

Melting point:

Isomer	Melting Range (°C)
L-T4	233 - 235 (decomp)
L-T4	235 - 236 (decomp)
D-T4	237 (decomp)
L-T4	236 (corr)

pKa: The apparent pKa of the phenolic hydroxyl, carboxyl and amino functions has been reported:

Function	pKa	pKa[a]
carboxyl	2.2	3.832
phenolic hydroxyl	6.7	8.085
amino	10.1	9.141

[a] In 75% dimethylsulfoxide-water and 0.1 M KNO_3
Titrant: potentiometric with sodium hydroxide

CLINICAL TRIALS

Thyroxine therapy is given to replace thyroid hormone secretion when it is deficient (hypothyroidism).

Studies of the effect of thyroxine replacement therapy on bone mineral density have given conflicting results; the reductions in bone mass reported by some have prompted recommendations that prescribed doses of thyroxine be reduced. The long-term effect of thyroxine treatment was examined in a large homogenous group of patients, all having undergone thyroidectomy for differentiated thyroid cancer with no history of other thyroid disorders.

Despite long-term thyroxine therapy [mean duration 7.9 (range 1 - 19) years] at doses [mean 191 (SD 50) mcg/day] that resulted in higher serum thyroxine and lower serum thyrotropin concentrations than in the controls, the patients showed no evidence of lower bone mineral density than the controls at any site. Nor was bone mineral density correlated with dose, duration of therapy or cumulative intake, or with tests of thyroid function.

In a study to evaluate the effects of pregnancy on thyroxine requirements, a retrospective review of 12 women receiving treatment for primary hypothyroidism before, during, and after pregnancy was conducted.

In all patients, the serum thyrotropin level increased during pregnancy. Because of high thyrotropin levels, the thyroxine dose was increased in 9 of the 12 patients. The results indicate that the need for thyroxine increases in many women with primary hypothyroidism when they are pregnant.

The longitudinal response in 43 infants with congenital primary hypothyroidism during the first year of levothyroxine therapy was evaluated. Diagnosis was confirmed by serum thyroid hormone measurements by 4 weeks of age in 38 infants and between 40 and 80 days of age in the remainder.

Levothyroxine therapy, at an average dose of 10 to 14 mcg/kg/day, was begun immediately after diagnosis, and serum concentrations of total thyroxine, triiodothyronine, reverse triiodothyronine and TSH were determined serially. Serum concentration of total and free thyroxine became normal within 1 week of the start of therapy in all groups. Despite a similarly mild degree of hypothyroidism at diagnosis in infants with dyshormonogenesis or with ectopia or hypoplasia, those with dyshormonogenesis had a more sensitive response to initial thyroid hormone replacement therapy than did patients with thyroid dysgenesis, as judged by levothyroxine dose

and TSH suppression. It was concluded that prompt restoration of clinical and biochemical euthyroidism during early infancy with doses of levothyroxine between 10 to 14 mcg/kg/day was a safe and effective method of therapy for children with congenital hypothyroidism.

DETAILED PHARMACOLOGY

Pharmacodynamic Properties

The normal thyroid gland secretes sufficient amounts of the thyroid hormones, triiodothyronine (T_3) and tetraiodothyronine (T_4, thyroxine), to maintain normal growth and development, normal body temperature, and normal energy levels. These hormones contain 59% and 65%, respectively, of iodine as an essential part of the molecule. Nearly all of iodide (I-) intake is via the gastrointestinal tract from food, water, or medication. This ingested iodide is rapidly absorbed and enters an extracellular fluid pool. The thyroid gland removes about 75 mcg a day from this pool for hormone secretion, and the balance is excreted in the urine. If iodide intake is increased, the fractional iodine uptake by the thyroid is diminished.

Once taken up by the thyroid gland, iodide undergoes a series of enzymatic reactions that convert it into active thyroid hormone. The first step is the transport of iodide into the thyroid gland, called iodide trapping. Iodide is then oxidized by thyroidal peroxidase to iodine, in which form it rapidly iodinates tyrosine residues within the thyroglobulin molecule to form monoiodotyrosine and diiodotyrosine. This process is called iodide organification. Thyroidal peroxidase is transiently blocked by high levels of intrathyroidal iodide and blocked by thioamide drugs. Two molecules of diiodotyrosine combine within the thyroglobulin molecule to form I-thyroxine (T_4). One molecule of monoiodotyrosine and one molecule of diiodotyrosine combine to form T_3. In addition to thyroglobulin, other proteins within the gland may be iodinated, but these iodoproteins do not have hormonal activity. Thyroid hormones are released from thyroglobulin by exocytosis and proteolysis of thyroglobulin at the apical colloid border. The colloid droplets of thyroglobulin merge with lysosomes containing proteolytic enzymes, which hydrolyze thyroglobulin and release T_4 and T_3. The monoiodotyrosine and diiodotyrosine are deiodinated within the gland, and the iodine is reutilized. In addition to T_4 and T_3, small amounts of thyroglobulin, tyrosine and iodide are secreted. This process of proteolysis is also blocked by high levels of intrathyroidal iodide. The ratio of T_4 to T_3 within thyroglobulin is approximately 5:1, so that most of the hormone released is thyroxine. Most of the T_3 circulating in the blood is derived from peripheral metabolism of thyroxine.

The mechanisms by which thyroid hormones exert their physiologic action are not well understood. Free forms of thyroid hormones T_4 and T_3, dissociated from thyroid binding proteins, enter the cell by diffusion or possibly by active transport. Within the cell, T_4 is converted to T_3. T_3 enters the nucleus and binds to a T_3 receptor protein.

Most of the effects of thyroid on metabolic processes appear to be mediated by activation of nuclear receptors that lead to increased formation of RNA and subsequent protein synthesis.

Large numbers of thyroid hormone receptors are found in most hormone-responsive tissues (pituitary, liver, kidney, heart, skeletal muscle, lung, and intestine). The brain, which lacks an anabolic response to T_3, contains an intermediate number of receptors. The number of receptors may be altered to preserve body homeostasis.

Some of the widespread effects of thyroid hormones in the body are secondary to stimulation of oxygen consumption, although the hormones also affect growth and development in mammals, help regulate lipid metabolism, and increase the absorption of carbohydrates from the intestine.

Thyroid hormone is critical for nervous, skeletal, and reproductive tissues. Its effects depend upon protein synthesis as well as potentiation of the secretion and action of growth hormone. Thyroid deprivation in early life results in irreversible mental retardation and dwarfism.

Pharmacokinetic Properties and Bioavailability

Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated.

More than 99% of circulating hormones are bound to serum proteins, including thyroxine-binding globulin (TBG), thyroxine-binding pre-albumin (TBPA), and albumin (TBA). T_4 is more extensively and firmly bound to serum proteins than is T_3. Only unbound thyroid hormone is metabolically active. The higher affinity of TBG and TBPA for T_4 partly explains the higher serum levels, slower metabolic clearance, and longer serum half-life of this hormone. Certain drugs and physiologic conditions can alter the binding of thyroid hormones to serum proteins and/or the concentrations of the serum proteins available for thyroid hormone binding. These effects must be considered when interpreting the results of thyroid function tests. (**See DRUG INTERACTIONS, Drug-Laboratory Interactions**.)

T_4 is eliminated slowly from the body, with a half-life of 6 to 7 days. T_3 has a half-life of 1 to 2 days. The liver is the major site of degradation for both hormones. T_4 and T_3 are conjugated with glucuronic and sulfuric acids and excreted in the bile. There is an enterhepatic circulation of thyroid hormones, as they are liberated by hydrolysis in the intestine and reabsorbed. A portion of the conjugated material reaches the colon unchanged, is hydrolyzed there, and is eliminated as free compounds in the feces. In man, approximately 20 to 40% of T_4 is eliminated in the stool. About 70% of the T_4 secreted daily is deiodonated to yield equal amounts of T_3 and rT_3. Subsequent deiodination of T_3 and rT_3 yields multiple forms of diiodothyronine. A number of other minor T_4 metabolites have also been identified. Although some of these metabolites have biological activity, their overall contribution to the therapeutic effect of T_4 is minimal.
It has been reported that approximately 80% of endogenous T_3 is obtained by metabolism of T_4 in the liver and kidneys. Exogenously administered T_4 may suppress T_3 serum levels in healthy individuals.

TOXICOLOGY

Repeated-dose Toxicity

Excess thyroid hormone decreases bone mineral density (BMD). The effect of thyroid hormone excess on vertebral and femoral BMD and the role of hypogonadism in modulating this effect were studied in a rat model. The potential role of calcitonin in preventing thyroid hormone-associated bone loss was also investigated. A total of 40 male Sprague-Dawley rats were divided into four groups. Groups 1 and 2 were orchidectomized; groups 3 and 4 were sham operated. Groups 1 and 3 received 20 mcg intraperitoneal L-thyroxine per 100 g body weight daily for 3 weeks; groups 2 and 4 received vehicle IP. Another 40 rats were divided into four groups with groups 1 and 2 receiving L-thyroxine and 3 and 4 receiving calcitonin, 2.5 U per 100 g body weight, subcutaneously for 3 weeks. Bone mineral density of the L4 and 5 and the right femur

were measured by dual-energy x-ray absorptiometry at baseline and at the end of the study. Orchidectomy decreased femoral ($p < 0.05$) but not lumbar BMD. The administration of excess L-Thyroxine decreased femoral (cortical) BMD in both sham operated ($p < 0.05$) and orchidectomized rats ($p < 0.05$) without affecting lumbar (trabecular) BMD. Calcitonin increased lumbar BMD in both vehicle ($p < 0.001$) and L-thyroxine treated rats ($p < 0.001$). However, calcitonin did not affect femoral BMD in vehicle-treated rats and did not prevent the L-thyroxine-induced femoral bone loss. Serum tartrate-resistant acid phosphatase (TRAP) was increased in the L-thyroxine-treated ($p < 0.001$) and the orchidectomized ($p < 0.05$) rats. Calcitonin had no effect on TRAP activity and did not prevent the L-Thyroxine-induced increase in TRAP. Neither excess L-thyroxine nor orchidectomy affect osteocalcin concentrations. Calcitonin decreased serum osteocalcin concentrations, alone ($p < 0.05$) and in the presence of excess L-thyroxine ($p < 0.05$). It was concluded that large doses of L-thyroxine administered to the rat preferentially decreased femoral BMD. Short-term hypogonadism decreases femoral but not lumbar BMD and does not make the lumbar spine more susceptible to the potential thyroid hormone-induced bone loss. Calcitonin increases lumbar BMD but does not prevent the thyroid hormone-induced decrease in femoral BMD.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Few published toxicology studies of levothyroxine have been performed to evaluate any carcinogenic potential, mutagenic potential, or impairment of fertility. Synthetic levothyroxine is identical to that produced by the human thyroid gland and so, effects of this nature would not be expected unless administered in excessive doses.

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PART III: CONSUMER INFORMATION

Pr LEVOTHYROXINE SODIUM FOR INJECTION

(Levothyroxine Sodium for Injection)

This leaflet is part III of a three-part "Product Monograph" published when LEVOTHYROXINE SODIUM FOR INJECTION was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LEVOTHYROXINE SODIUM FOR INJECTION. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Levothyroxine is a synthetic thyroid hormone used for treatment of hypothyroidism (low thyroid hormones secretion).

What it does:

The levothyroxine in LEVOTHYROXINE SODIUM FOR INJECTION is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient (temporary) hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis). LEVOTHYROXINE SODIUM FOR INJECTION is used as a substitute for oral levothyroxine tablets when rapid treatment is required or when oral medication cannot be taken.

When it should not be used:

LEVOTHYROXINE SODIUM FOR INJECTION should not be used in patients:

- with overactive thyroid glands;
- with uncorrected adrenal insufficiency (not enough adrenal hormones);
- with acute myocardial infarction (heart attack);
- who are pregnant and taking drugs for hyperthyroidism;
- who are sensitivity to any of the ingredients.

What the medicinal ingredient is:

Levothyroxine sodium.

What the nonmedicinal ingredients are:

Mannitol, dibasic sodium phosphate heptahydrate, and sodium hydroxide.

What dosage forms it comes in:

LEVOTHYROXINE SODIUM FOR INJECTION is available as a sterile lyophilized powder for reconstitution.

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 patients with normal thyroid function, doses within the range of daily hormonal requirements are ineffective for weight reduction.
- Larger doses may produce serious or even life-threatening toxic effects, particularly when taken with products used for their appetite suppressing effects.

Tell your doctor before and while using LEVOTHYROXINE SODIUM FOR INJECTION:

- if you are allergic to any foods or medicines;
- if you are taking any other prescription, non-prescription (over-the-counter) medications, or herbal/alternative supplements;
- if you have, either presently or in the past, any other medical problems, whether or not you have received treatment for them (especially hardening of the arteries, irregular heartbeat, heart failure, coronary insufficiency, heart disease, high blood pressure, osteoporosis, blood clotting disorders, or history of thyroid, adrenal, or pituitary gland problems);
- if you have diabetes, your dose of insulin or oral antidiabetic agent may need to be changed after starting LEVOTHYROXINE SODIUM FOR INJECTION. You should monitor your blood and urinary glucose levels as directed by your doctor and report any changes to your doctor immediately;
- if you are taking an oral anticoagulant drug (blood thinner) such as warfarin, your dose may need to be changed after starting LEVOTHYROXINE SODIUM FOR INJECTION. Your coagulation status should be checked often to determine if a change in dose is required;
- if you are or intend to become pregnant, or are breast-feeding. Your dose of this medicine will likely have to be increased while you are pregnant.

Other Precautions:

You should inform your doctor or dentist that you are taking LEVOTHYROXINE SODIUM FOR INJECTION before having any kind of surgery.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with LEVOTHYROXINE SODIUM FOR INJECTION:

- oral anticoagulants, used as blood thinners;
- digitalis glycosides (e.g., digoxin), a heart medication;

- antidiabetic agents (insulin or oral hypoglycemic drugs), used to normalize blood sugar;
- beta-adrenergic antagonists, also called beta-blockers (e.g., metoprolol, atenolol, bisoprolol, propranolol), used to decrease heart rate;
- glucocorticoids (corticosteroids), used to decrease inflammation;
- amiodarone, used to normalize heart rhythm;
- diazepam (e.g. Valium), used to treat seizure, anxiety and other neurological diseases;
- antidepressants;
- lithium, used to treat bipolar disease;
- beta-sympatholytics/sympathomimetics, used to stimulate the heart and treat breathing problems [e.g.,Ventolin (salbutamol)];
- propylthiouracil (PTU), used to treat thyroid disease;
- sulphonamides, used to treat infection;
- methimazole, used to reduce the production of thyroid hormone;
- iodide, iodine containing contrast media;
- coumarin derivatives, used as blood thinners;
- ketamine, used mainly for anesthesia;
- phenytoin, used to prevent seizures;
- salicylates, used to relieve pain;
- dicumarol, used as a blood thinner;
- furosemide, known as water pill, helps eliminate excess water;
- clofibrate, used to lower cholesterol;
- sevelamer used to decrease high phosphate levels;
- tyrosine kinase inhibitors, used to treat some types of cancers;
- estrogen contraceptives, hormone replacement therapy;
- barbiturates (e.g. phenobarbital), taken for their calming or sleep-inducing effect;
- carbamazepine, used to treat seizure/fit and nerve pain;
- proton pump inhibitors, used to reduce excessive gastric acid secretion.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will decide and adjust your dosage depending upon your response to the medication. The starting dose of levothyroxine sodium, the frequency of dose adjustment, and the optimal full replacement dose must be individualized for every patient, and will be influenced by such factors as age, weight, cardiovascular status, presence of other illness, and the severity and duration of hypothyroid symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Adverse reactions associated with LEVOTHYROXINE SODIUM FOR INJECTION are primarily due to therapeutic overdosage.

- incomplete bone growth
- hair loss
- menstrual irregularities, and impaired fertility
- osteoporosis

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
chest pain, rapid or irregular heartbeat, palpitations, increased blood pressure, heart failure, angina, heart attack, shortness of breath			✓
elevations in liver enzymes		✓	
decreased bone mineral density		✓	
hypersensitivity, hives or skin rash, angioedema		✓	
seizures			✓
fatigue, sleeplessness, restlessness	✓		
change in appetite, weight gain or loss	✓		
heat intolerance, fever, flushing		✓	
hyperactivity, nervousness, anxiety, irritability, emotional lability		✓	
tremors, muscle weakness, abdominal and leg cramps		✓	
excessive sweating		✓	
headache	✓		
diarrhea, vomiting	✓		

This is not a complete list of side effects. For any unexpected effects while taking LEVOTHYROXINE SODIUM FOR INJECTION, contact your doctor or pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting ((https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Store at room temperature (15 to 30°C), protected from light.

Use immediately after reconstitution. The reconstituted drug product is stable for a period of 4 hours at 25°C. Discard any unused portion.

Keep out of reach and sight of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting **AVIR Pharma Inc.** at 1-800-363-7988.

This leaflet was prepared by

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