PRODUCT MONOGRAPH

PrELTROXIN®

levothyroxine sodium tablet, BP
50, 100, 150, 200 and 300 mcg

Thyroid hormone

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablet - 50, 100, 150, 200 and 300 mcg	lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ELTROXIN® (levothyroxine sodium) is indicated as:

- replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis;

- Specific indications are: primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism

- a pituitary TSH suppressant in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter , and in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

CONTRAINDICATIONS

ELTROXIN® (levothyroxine sodium) is contraindicated in:

- Patients with an apparent hypersensitivity to thyroid hormones or any of the inactive product constituents.
- Patients with untreated subclinical (suppressed serum TSH with normal T_3 and T_4 levels) or overt thyrotoxicosis of any etiology.
- Patients with acute myocardial infarction.
- Patients with uncorrected adrenal insufficiency, as thyroid hormones increase tissue demands for adrenocortical hormones and may thereby precipitate acute adrenal crisis (see WARNINGS AND PRECAUTIONS).

Serious Warnings and Precautions

Thyroid hormones, including ELTROXIN®, 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.

WARNINGS AND PRECAUTIONS

General

ELTROXIN® (levothyroxine sodium) has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under- treatment. 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).

The bioavailability of levothyroxine may differ to some extent among marketed brands. Once the patient is stabilized on a particular brand of levothyroxine sodium caution should be exercised when a change in drug product brand is implemented.

It has been shown that differences in formulations of levothyroxine, despite an identical content of active ingredient, may be associated with differences in fractional gastrointestinal absorption. These differences may not be observed

through measurement of total T_3 and T_4 serum levels. It is therefore, recommended that patients who are switched from one levothyroxine formulation to another be retitrated to the desired thyroid function. Accuracy in retitration can best be achieved by using sensitive thyrotropin assays.

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.

Lithium blocks the TSH-mediated release of T_4 and T_3. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual levothyroxine sodium dose may be required.

Cardiovascular

Levothyroxine sodium should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, and hypertension, and in the elderly who have a greater likelihood of occult cardiac disease. In these patients, levothyroxine sodium therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac diseases (see WARNINGS AND PRECAUTIONS-Special Populations-Geriatrics and DOSAGE AND ADMINISTRATION). If cardiac symptoms develop or worsen, the levothyroxine sodium dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Over-treatment 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 sodium 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 thyroid hormone and sympathomimetic agents to patients with coronary artery disease may increase the risk of coronary insufficiency.

Endocrine and Metabolism

Thyroid hormones, either alone or together 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.

Patients treated concomitantly with ELTROXIN and orlistat should be monitored for changes in thyroid function (see DRUG INTERACTIONS). Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism may involve a decreased absorption of iodine salts and/or levothyroxine.

Effects on Bone Mineral Density

In women, long-term levothyroxine therapy has been associated with increased bone

resorption, thereby decreasing bone mineral density, especially in postmenopausal women on greater 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 phosphorous, 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.

Patients with Nontoxic Diffuse Goiter or Nodular Thyroid Disease

In patients with non-toxic diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitating overt thyrotoxicosis (see CONTRAINDICATIONS). If the serum TSH level is not suppressed, levothyroxine sodium should be used with caution in conjunction with careful monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential associated adverse cardiovascular signs and symptoms of hyperthyroidism.

Associated Endocrine Disorders

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.

Autoimmune Polyglandular Syndrome

Use of levothyroxine sodium in patients with concomitant diabetes mellitus, diabetes insipidus or adrenal cortical insufficiency may aggravate the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases may therefore be required. Treatment of myxedema coma may require simultaneous administration of glucocorticoids (see DOSAGE AND ADMINISTRATION).

Hematologic

T_4 enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both levothyroxine sodium and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly.

Sexual Function/Reproduction

The use of levothyroxine sodium is also unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

Special Populations

Pregnant Women

Studies in pregnant women have not shown that levothyroxine sodium increases the risk of fetal abnormalities if administered during pregnancy. If levothyroxine sodium is used during pregnancy, the possibility of fetal harm appears remote.

Thyroid hormones cross the placental barrier to some extent. T_4 levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of T_4 may not prevent in utero hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, preeclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. On the basis of current knowledge, levothyroxine sodium should therefore not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T_4 concentrations may decrease and TSH concentrations may increase to values outside normal ranges. Postpartum values are similar to preconception values. Elevations in TSH may occur as early as the fourth week of gestation.

Pregnant women who are maintained on levothyroxine sodium should have their TSH measured periodically. An elevated TSH should be corrected by an increase in levothyroxine sodium dose. After pregnancy, the dose can be decreased to the optimal preconception dose. A serum TSH level should be obtained six to eight weeks postpartum.

Nursing Women
Minimal amounts of thyroid hormones are excreted in human milk. Thyroid hormones are not associated with serious adverse reactions and do not have known tumorigenic potential. While caution should be exercised when levothyroxine sodium is administered to a nursing woman, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.

Pediatrics (All ages including neonates)
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 to prevent deleterious neonatal thyroid hormone deficiency effects on intelligence, overall growth, and development. Treatment should be initiated immediately upon diagnosis and generally maintained for life. The therapeutic goal is to maintain serum total T_4 or FT_4 in the upper half of the normal range and serum TSH in the normal range.

An initial starting dose of 10 to 15 mcg/kg/day (ages 0 to 3 months) will generally increase serum T_4 concentrations to the upper half of the normal range in less than 3 weeks. Clinical assessment of growth, development, and thyroid status should be monitored frequently. In most cases, the levothyroxine sodium dose per body weight will decrease as the patient grows through infancy and childhood (see DOSAGE AND ADMINISTRATION-Recommended Dose and Dosage Adjustment-Pediatric Dosage-

Table 2). Prolonged use of large doses in infants may be associated with temperament problems, which appear to be transient.

Thyroid function tests (serum total T_4 or FT_4, and TSH) should be monitored closely and used to determine the adequacy of levothyroxine sodium therapy. Serum T_4 normalization is usually followed by a rapid decline in TSH. Nevertheless, TSH normalization may lag behind T_4 normalization by 2 to 3 months or longer. The relative serum TSH elevation is more marked in the early months, but can persist to some degree throughout life. In rare patients TSH remains relatively elevated despite clinical euthyroidism and age-specific normal total T_4 or FT_4 levels. Increasing the levothyroxine sodium dosage to suppress TSH into the normal range may produce overtreatment, with an elevated serum T_4 and clinical features of hyperthyroidism including: irritability, increased appetite with diarrhea, and sleeplessness. Another risk of prolonged overtreatment in infants is premature cranial synostosis.

Acquired hypothyroidism

The initial levothyroxine sodium dose varies with age and body weight, and should be adjusted to maintain serum total T_4 or free T_4 levels in the upper half of the normal range. In general, unless there are overriding clinical concerns, children should be started on a full replacement dose. Children with underlying heart disease should be started at lower dosages, with careful upward titration. Children with severe, longstanding hypothyroidism may also be started on a lower initial dose followed by an upward titration, attempting to avoid premature epiphyseal closure. The recommended dose per body weight decreases with age (see DOSAGE AND ADMINISTRATION-Recommended Dose and Dosage Adjustment-Pediatric Dosage-Table 2).

Treated children may resume growth at a greater than normal rate (period of transient catch-up growth). In some cases the catch-up may be adequate to normalize growth. However, severe and prolonged hypothyroidism may reduce adult height. Excessive thyroxine replacement may initiate accelerated bone maturation, producing disproportionate skeletal age advancement and shortened adult stature.

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 reevaluation 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 sodium 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 sodium treatment should be discontinued for another 30-day trial period followed by repeat serum T_4 and TSH

testing.

Geriatrics (> 50 years of age)
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 and DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests
Treatment of patients with levothyroxine sodium requires periodic assessment of thyroid status by appropriate laboratory tests and clinical evaluation. Selection of appropriate tests for the diagnosis and management of thyroid disorders depends on patient variables such as presenting signs and symptoms, pregnancy, and concomitant medications. A measurement of free T_4 and TSH levels, using a sensitive TSH assay, are recommended to confirm a diagnosis of thyroid disease. Normal ranges for these parameters are age-specific in newborns and younger children.

TSH alone or initially may be useful for thyroid disease screening and for monitoring therapy for primary hypothyroidism as a linear inverse correlation exists between serum TSH and free T_4. Measurement of total serum T_4 and T_3, resin T_3 uptake, and free T_3 concentrations may also be useful. Antithyroid microsomal antibodies are an indicator of autoimmune thyroid disease. Positive microsomal antibody presence in an euthyroid patient is a major risk factor for the development of hypothyroidism. An elevated serum TSH in the presence of a normal T_4 may indicate subclinical hypothyroidism. Intracellular resistance to thyroid hormone is quite rare, and is suggested by clinical signs and symptoms of hypothyroidism in the presence of high serum T_4 levels. 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. Adequacy of levothyroxine sodium therapy for congenital and acquired pediatric hypothyroidism should be assessed by measuring serum total T_4 or free T_4; these should be maintained in the upper half of the normal range. In congenital hypothyroidism, serum TSH normalization may lag behind serum T_4 normalization by 2 to 3 months or longer. In rare patients, serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal T_4 or free T_4 levels. (See WARNINGS AND PRECAUTIONS-Special Populations-Pediatrics)

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 sodium for established indications should not discontinue therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions other than those indicative of thyrotoxicosis as a result of therapeutic overdosage, either initially or during the maintenance periods, are rare (see OVERDOSAGE). Seizures have been reported rarely with the institution of levothyroxine sodium therapy. Pseudotumor cerebri and slipped capital femoral epiphysis have also been reported in children receiving levothyroxine therapy. Over treatment in children may result in craniosynostosis and premature closure of the epiphyses with resultant compromised adult height.

Inadequate doses of ELTROXIN® (levothyroxine sodium) may produce or fail to resolve symptoms of hypothyroidism. Hair loss may occur during the initial months of therapy, but is generally transient. The incidence of continued hair loss is unknown.

Adverse reactions associated with levothyroxine sodium are primarily those of hyperthyroidism due to therapeutic overdosage (see WARNINGS AND PRECAUTIONS and OVERDOSAGE). They include the following:

General:	fatigue, increased appetite, weight loss, heat intolerance, fever, and excessive sweating;
Cardiovascular System:	palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction and cardiac arrest;
Central Nervous System:	headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, and insomnia;
Dermatologic:	hair loss, flushing;
Endocrine System:	decreased bone mineral density;
Gastrointestinal System:	diarrhea, vomiting, abdominal cramps, and elevations in liver function tests;
Musculoskeletal System:	tremors, muscle weakness;
Reproductive System:	menstrual irregularities, impaired fertility;
Respiratory System:	dyspnea.

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

The magnitude and relative clinical importance of the effects noted below are likely to be patient-specific and may vary by such factors as age, gender, race, intercurrent illnesses, dose of either agents, additional concomitant medications, and timing of drug administration. Any agent that alters thyroid hormone synthesis, secretion, distribution, effect on target tissues, metabolism, or elimination may alter the optimal therapeutic dose of ELTROXIN® (levothyroxine sodium).

Drug-Drug Interactions

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 sodium. 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.

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 or 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

Drug or Drug Class	Effect
Drug-Thyroidal Axis Interactions Drugs that may reduce TSH secretion - the reduction is not sustained; therefore, hypothyroidism does not occur	
Dopamine/Dopamine Agonists Glucocorticoids Octreotide	Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: Dopamine (greater than or equal to 1 mcg/kg/min); Glucocorticoids (hydrocortisone greater than or equal to 100 mg/day or equivalent); Octreotide (greater than 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 Thioamides - Methimazole - Propylthiouracil (PTU) - Carbimazole Sulfonamides Tolbutamide	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimotos's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing radiographic contrast agents)	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Drugs that may decrease T_4 absorption, which may result in hypothyroidism	
Antacids - Aluminum & Magnesium Hydroxides -Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Cation Exchange Resins	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least four (4) hours apart from these agents. Patients treated concomitantly with orlistat and levothryoxine should be monitored for changes in thyroid function.

Drug or Drug Class	Effect
- Kayexalate Ferrous Sulfate Orlistat Sucralfate	
Drugs that may alter T_4 and T_3 serum transport - but FT_4 concentration remains normal; and therefore, the patient remains euthyroid	
Drugs that may increase serum TBG Concentration Clofibrate Estrogen-containing Oral Contraceptives Estrogens (oral) Heroin/Methadone 5-Fluorouracil Mitotane Tamoxifen	Drugs that may decrease serum TBG Concentration Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
Drugs that may cause protein-binding site replacement	
Furosemide (greater than 80 mg IV) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs - Fenamates - Phenylbutazone Salicylates (greater than 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in FT_4. Continued administration results in a decrease in Serum T_4 and normal FT_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum saliyclate concentrations, although total-T_4 levels may decrease by as much as 30%.
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	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.
Drugs that may decrease T_4 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists - (e.g., Propanolol greater than 160 mg/day) Glucocorticoids - (e.g., Dexamethasone greater than or equal to 4 mg/day) Propylthiouracil (PTU)	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 propanolol (greater than 160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid

Drug or Drug Class	Effect
	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	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)	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	Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.
Cardiac glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.
Cytokines - Interferon-alpha - Interleukin-2	Therapy with interferon-alpha 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-beta and-gamma have not been reported to cause thyroid dysfunction.

Drug or Drug Class	Effect
Growth Hormones - Somatrem - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
HMG-CoA reductase inhibitors (statins) - Lovastatin - Simvastatin	Some statins may increase thyroid hormone requirements. It is unknown if this occurs with all statins. Close monitoring of thyroid function and appropriate thyroxine dose adjustments may be necessary when thyroxine and statins are co-prescribed.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators - (e.g., Theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic agents	Thyroid hormones may reduce the uptake of ^{123}I, ^{131}I, and ^{99m}Tc.
Sympathomimetics	Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Chloral Hydrate Diazepam Ethionamide Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.

Anticoagulants

Levothyroxine levels increase 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 sodium 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 sodium. 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).

Orlistat

Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism, although not proven, may involve a decreased absorption of iodine salts and/or levothyroxine. Patients treated concomitantly with ELTROXIN and orlistat should be monitored for changes in thyroid function.

Drug-Food Interactions
Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, calcium and calcium-fortified orange juice, and dietary fibre may bind and decrease the absorption of levothyroxine sodium from the gastrointestinal tract.

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 DRUG INTERACTIONS).

1. Changes in TBG concentration should be taken into consideration when interpreting T_4 and T_3 values. Drugs such as estrogens and estrogen-containing oral contraceptives increase serum TBG concentrations. TBG concentrations may also be increased during pregnancy, in infectious hepatitis and acute intermittent porphyria. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroxine-binding- globulinemias have been described. The incidence of TBG deficiency is approximately 1 in 9000. Certain drugs such as salicylates inhibit the protein-binding of T_4. In such cases, the unbound (free) hormone should be measured.

2. Persistent clinical and laboratory evidence of hypothyroidism despite an adequate replacement dose suggests either poor patient compliance, impaired absorption, drug interactions, or decreased potency of the preparation due to improper storage.

DOSAGE AND ADMINISTRATION

Dosing Considerations
The dosage and rate of administration of ELTROXIN® (levothyroxine sodium) is determined by the indication, and must in every case be individualized according to patient response and laboratory findings.

Adult Dosage

Hypothyroidism
The goal of therapy for primary hypothyroidism is to achieve and maintain a clinical and biochemical euthyroid state with consequent resolution of hypothyroid signs and symptoms. The starting dose of levothyroxine sodium the frequency of dose titration, 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.

In patients with hypothyroidism resulting from pituitary or hypothalamic disease, the possibility of secondary adrenal insufficiency should be considered, and if present, treated with glucocorticoids prior to initiation of levothyroxine sodium. The adequacy of levothyroxine sodium therapy should be assessed in these patients by measuring FT_4, which should be maintained in the upper half of the normal range, in addition to clinical assessment. Measurement of TSH is not a reliable indicator of response to therapy for this condition.

TSH Suppression in Thyroid Cancer and Thyroid Nodules

The rationale for TSH suppression therapy is that a reduction in TSH secretion may decrease the growth and function of abnormal thyroid tissue. Exogenous thyroid hormone may inhibit recurrence of tumour growth and may produce regression of metastases from well-differentiated (follicular and papillary) carcinoma of the thyroid. It is used as ancillary therapy of these conditions following surgery or radioactive iodine therapy. Medullary and anaplastic carcinoma of the thyroid is unresponsive to TSH suppression therapy. TSH suppression is also used in treating nontoxic solitary nodules and multinodular goiters.

No controlled studies have compared the various degrees of TSH suppression in the treatment of either benign or malignant thyroid nodular disease. Further, the effectiveness of TSH suppression for benign nodular disease is controversial. The dose of levothyroxine sodium used for TSH suppression should therefore be individualized by the nature of the disease, the patient being treated, and the desired clinical response, weighing the potential benefits of therapy against the risks of iatrogenic thyrotoxicosis. In general, levothyroxine sodium should be given in the smallest dose that will achieve the desired clinical response.

Pediatric Dosage

Congenital or acquired hypothyroidism

The levothyroxine sodium pediatric dosage varies with age and body weight. Levothyroxine sodium should be given at a dose that maintains T_4 or free T_4 in the upper half of the normal range and serum TSH in the normal range (See WARNINGS AND PRECAUTIONS-Special Populations-Pediatrics). Normalization of TSH may lag significantly behind T_4 in some infants. In general, despite the smaller body size of children, the dosage (on a weight basis) required to sustain full development and general thriving is higher than in adults (see Table 2).

Recommended Dose and Dosage Adjustment

Adult Dosage

Hypothyroidism

The usual full replacement dose of levothyroxine sodium for younger, healthy adults is approximately 1.7 mcg/kg/day administered once daily. In the elderly, the full replacement dose may be altered by decreases in T_4 metabolism and levothyroxine sodium absorption. Older patients may require less than 1 mcg/kg/day. Children generally require higher doses (see Pediatric Dosage). Women who are maintained on levothyroxine sodium during pregnancy may require increased doses (see WARNINGS AND PRECAUTIONS-Special Populations-Pregnant Women).

Therapy is usually initiated in younger, healthy adults at the anticipated full replacement dose. Clinical and laboratory evaluations should be performed at 6 to 8 week intervals (2 to 3 weeks in severely hypothyroid patients), and the dosage adjusted until the serum TSH concentration is normalized and signs and symptoms resolve. In older patients or in younger patients with a history of cardiovascular disease, the starting dose should be lowered and gradually increased every 3 to 6 weeks until TSH is normalized and signs and symptoms resolve. If cardiac symptoms develop or worsen, the cardiac disease should be evaluated and the dose of levothyroxine sodium reduced. Rarely, worsening angina or other signs of cardiac ischemia may prevent achieving a TSH in the normal range.

Treatment of subclinical hypothyroidism may require lower than usual replacement doses, e.g. 1.0 mcg/kg/day. Patients for whom treatment is not initiated should be monitored yearly for changes in clinical status, TSH, and thyroid antibodies.

Few patients require doses greater than 200 mcg/day. An inadequate response to daily doses of 300 to 400 mcg/day is rare, and may suggest malabsorption, poor patient compliance, and/or drug interactions.

Once optimal replacement is achieved, clinical and laboratory evaluations should be conducted at least annually or whenever warranted by a change in patient status. Levothyroxine sodium products from different manufacturers should not be used interchangeably unless retesting of the patient and retitration of the dosage, as necessary, accompanies the product switch.

Myxedema Coma

Myxedema coma represents the extreme expression of severe hypothyroidism and is considered a 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.

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, such as levothyroxine sodium are not recommended to treat this condition. Thyroid hormone products formulated for intravenous administration should be administered.

TSH Suppression in Thyroid Cancer and Thyroid Nodules

For well-differentiated thyroid cancer, TSH is generally suppressed to less than 0.1 mU/L. Doses of levothyroxine sodium greater than 2 mcg/kg/day are usually required. The efficacy of TSH suppression in reducing the size of benign thyroid nodules and in preventing nodule regrowth after surgery is controversial. Nevertheless, when treatment with levothyroxine sodium is warranted, TSH is generally suppressed to a higher target range (e.g. 0.1 to 0.3 mU/L) than that employed for the treatment of thyroid cancer. Levothyroxine sodium therapy may also be considered for patients with nontoxic multinodular goiter who have a TSH in the normal range, to moderately suppress TSH (e.g. 0.1 to 0.3 mU/L).

Levothyroxine sodium should be administered with caution to patients in whom there is a suspicion of thyroid gland autonomy, in view of the fact that the effects of exogenous hormone administration will be additive to endogenous thyroid hormone production.

Pediatric Dosage

Congenital or acquired hypothyroidism

Therapy is usually initiated at the full replacement dose (see Table 2). Infants and neonates with very low (< 5 mcg/dL) or undetectable serum T_4 levels should be started at higher end of the dosage range (e.g. 50 mcg daily). A lower dose (e.g. 25 mcg daily) should be considered for neonates at risk of cardiac failure, increasing every few days until a full maintenance dose is reached. In children with severe, longstanding hypothyroidism, levothyroxine sodium should be initiated gradually, with an initial 25 mcg dose for two weeks, then increasing by 25 mcg every 2 to 4 weeks until the desired dose, based on serum T_4 and TSH levels, is achieved.

Table 2: Levothyroxine Sodium Dosing Guidelines for Pediatric Hypothyroidism

AGE	Daily Dose Per Kg Body Weight[a]
0-3 months	10-15 mcg/kg/day
3-6months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
> 12 years but growth and puberty incomplete	2-3 mcg/kg/day
Growth and puberty complete	1.6 – 1.7 mcg/kg/day

[a] The dose should be adjusted based on clinical response and laboratory parameters (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics).

Serum T_4 and TSH measurements should be evaluated at the following intervals, with subsequent dosage adjustments to normalize serum total T_4 or FT_4 and TSH:

2 and 4 weeks after therapy initiation,
every 1 to 2 months during the first year of life,
every 2 to 3 months between 1 and 3 years of age,
every 3 to 12 months thereafter until growth is completed

Evaluation at more frequent intervals is indicated when compliance is questioned or abnormal laboratory values are obtained. Patient evaluation is also advisable approximately 6 to 8 weeks after any change in levothyroxine sodium dose.

Missed Dose

If a scheduled daily dose is missed, the dose should be taken as soon as the patient remembers, unless it is almost time for the patient's next dose. Two doses should not be taken together. If more than two doses are missed, the patient should consult with their doctor.

Administration

Pediatrics

Levothyroxine sodium tablets may be given to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount of water (5 to 10 mL), breast milk or non-soybean based formula. The suspension can be given by spoon or dropper. DO NOT STORE THE SUSPENSION FOR ANY PERIOD OF TIME. The crushed tablet may also be sprinkled over a small amount of food, such as apple sauce. Foods or formula containing large amounts of soybean, fibre, or iron should not be used for administering levothyroxine sodium.

OVERDOSAGE

Signs and Symptoms

Excessive doses of ELTROXIN® (levothyroxine sodium) result in a hypermetabolic state indistinguishable from thyrotoxicosis of endogenous origin. Signs and symptoms of thyrotoxicosis include exophthalmic goiter, weight loss, increased appetite, palpitations, nervousness, diarrhea, abdominal cramps, sweating, tachycardia, increased pulse and blood pressure, cardiac arrhythmias, angina pectoris, tremors, insomnia, heat intolerance, fever, and menstrual irregularities. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures have occurred in a child ingesting 18 mg of levothyroxine. Symptoms are not always evident or may not appear until several days after ingestion of levothyroxine sodium.

Treatment of Overdosage

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

In the treatment of acute massive levothyroxine sodium overdosage, symptomatic and supportive therapy should be instituted immediately. Treatment is aimed at reducing gastrointestinal absorption and counteracting central and peripheral effects, mainly those of increased sympathetic activity. Cholestyramine and activated charcoal have also been used to decrease levothyroxine sodium absorption. Beta-receptor antagonists, particularly propranolol, are useful in counteracting many of the effects of increased central and peripheral sympathetic activity, especially when no contraindications exist for its 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, carbimazole, or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones. Cardiac glycosides may be administered if congestive heart failure develops. Glucocorticoids may be administered 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. Since T_4 is extensively protein bound, very little drug will be removed by dialysis.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The synthesis and secretion of the major thyroid hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), from the normally functioning thyroid gland are regulated by complex feedback mechanisms of the hypothalamic-pituitary-thyroid axis. The thyroid gland is stimulated to secrete thyroid hormones by the action of thyrotropin (thyroid stimulating hormone, TSH), which is produced in the anterior pituitary gland. TSH

secretion is in turn controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus, circulating thyroid hormones, and possibly other mechanisms. Thyroid hormones circulating in the blood act as feedback inhibitors of both TSH and TRH secretion. Thus, when serum concentrations of T_3 and T_4 are increased, secretion of TSH and TRH decreases. Conversely, when serum thyroid hormone concentrations are decreased, secretion of TSH and TRH is increased. Administration of exogenous thyroid hormones to euthyroid individuals results in suppression of endogenous thyroid hormone secretion.

The mechanisms by which thyroid hormones exert their physiologic actions have not been completely elucidated, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T_4 and T_3 are transported into cells by passive and active mechanisms. T_3 in cell cytoplasm and T_3 generated from T_4 within the cell diffuse into the nucleus and bind to thyroid receptor proteins, which appear to be primarily attached to DNA. Receptor binding leads to activation or repression of DNA transcription, thereby altering the amounts of mRNA and resultant proteins. Changes in protein concentrations are responsible for the metabolic changes observed in organs and tissues.

Thyroid hormones enhance oxygen consumption of most body tissues and increase the basal metabolic rate and metabolism of carbohydrates, lipids, and proteins. Thus, they exert a profound influence on every organ system and are of particular importance in the development of the central nervous system. Thyroid hormones also appear to have direct effects on tissues, such as increased myocardial contractility and decreased systemic vascular resistance.

The physiologic effects of thyroid hormones are produced primarily by T_3, a large portion of which (approximately 80%) is derived from the deiodination of T_4 in peripheral tissues. About 70 to 90 percent of peripheral T_3 is produced by monodeiodination of T_4 at the 5 position (outer ring). Peripheral monodeiodination of T_4 at the 5 position (inner ring) results in the formation of reverse triiodothyronine (rT_3), which is calorigenically inactive.

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.

Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, Hashimoto's thyroiditis, multinodular goiter and, as adjunctive therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (see INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pharmacokinetics

Absorption

Few clinical studies have evaluated the kinetics of orally administered thyroid hormone. In animals, the most active sites of absorption appear to be the proximal and mid-jejunum. T_4 is not absorbed from the stomach and little, if any, drug is absorbed from the duodenum. There seems to be no absorption of T_4 from the distal colon in animals. A number of human studies have confirmed the importance of an intact jejunum and ileum for T_4 absorption and have shown some absorption from the duodenum. Studies involving radioiodinated T_4 fecal tracer excretion methods, equilibration, and AUC methods have shown that absorption varies from 48 to 80 percent of the administered dose. The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes, such as sprue. Absorption may also decrease with age. The degree of T_4 absorption is dependent on the product formulation as well as on the character of the intestinal contents, the intestinal flora, including plasma protein and soluble dietary factors, which bind thyroid hormone, making it unavailable for diffusion. Decreased absorption may result from administration of infant soybean formula, ferrous sulfate, sodium polystyrene sulfonate, aluminum hydroxide, sucralfate, or bile acid sequestrants. T_4 absorption following intramuscular administration is variable. The relative bioavailability of levothyroxine sodium tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%.

Distribution

Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated. More than 99% of circulating hormones is bound to serum proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (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 elimination 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 WARNINGS AND PRECAUTIONS-Monitoring and Laboratory Test and DRUG INTERACTIONS)

Metabolism

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 enterohepatic 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 percent of T_4 is eliminated in the stool. About 70 percent of the T_4 secreted daily is deiodinated 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 biologic activity, their overall contribution to the therapeutic effect of T_4 is minimal.

Excretion
Thyroid hormones are primarily eliminated by the kidneys. T_4 is eliminated slowly from the body (see Table 3), with a half-life of 6 to 7 days. T_3 has a half-life of 1 to 2 days.

Table 3

Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients				
Hormone	**Ratio in Thyroglobulin**	**Biologic Potency**	**t½ (days)**	**Protein Binding (%)2**
Levothyroxine, T_4	10 to 20	14	6 to 7[1]	99.96
Liothyronine T_3	1		< 2	99.5

[1] Three to four days in hyperthyroidism, nine to ten days in hypothyroidism
[2] Includes TBG, TBPA, and TBA

STORAGE AND STABILITY

Store between 15ºC and 25ºC. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

ELTROXIN® Tablets are available in five different strengths:

ELTROXIN®Tablets 50 mcg:
White, scored, round tablets engraved with “50". Bottles of 500.

ELTROXIN® Tablets 100 mcg:
Yellow, scored, round tablets engraved with “100". Bottles of 500.

ELTROXIN® Tablets 150 mcg:
Blue, scored, round tablets engraved with “150". Bottles of 500.

ELTROXIN® Tablets 200 mcg:
Pink, scored, round tablets engraved with “200". Bottles of 500.

ELTROXIN® Tablets 300 mcg:
Green, scored, round tablets engraved with “300". Bottles of 100 and 500.

Composition

ELTROXIN® Tablets contain levothyroxine sodium and the following non-medicinal ingredients: acacia powder, corn starch, lactose, magnesium stearate and coloring agents:

50 mcg (white)	- none
100 mcg (yellow)	- colorcon yellow
150 mcg (blue)	- colorcon blue
200 mcg (pink)	- erythrosine
300 mcg (green)	- colorcon green

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

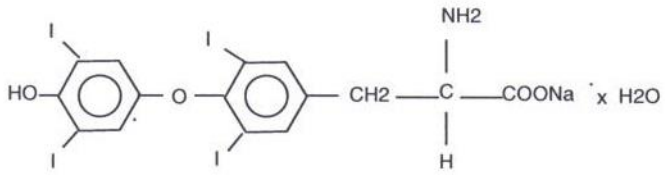
Proper name: levothyroxine sodium

Chemical name: L-Tyrosine, 0- (4-hydroxy-3,5-diiodophenyl)-3,5-diiodomonosodium salt, hydrate

Molecular formula and molecular mass: $C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$

798.86 (anhydrous)

Structural formula:



Physicochemical properties: Levothyroxine sodium is an odourless almost white to pale brownish yellow powder, or a fine, slightly coloured, crystalline powder. It is very slightly soluble in water; soluble in 250 parts of ethanol (96 per cent); practically insoluble in chloroform and in ether; soluble in solutions of the alkali hydroxides.

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PART III: CONSUMER INFORMATION

Pr ELTROXIN®
levothyroxine sodium tablet, BP

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

ABOUT THIS MEDICATION

What the medication is used for:
ELTROXIN® contains the active ingredient levothyroxine sodium which is the same as the hormone, thyroxine. Thyroxine and another hormone, liothyronine, are two hormones produced and released by the thyroid gland. These hormones are responsible for maintaining a normal rate of metabolism in the body.

In other areas of the body, thyroxine is converted into liothyronine, which is a more active form of thyroxine.

Hypothyroidism occurs when the thyroid gland is unable to produce normal amounts of thyroxine resulting in the level of thyroid hormones in the blood to decrease. The body cannot function properly without this hormone, resulting in poor growth, slow speech, lack of energy, weight gain, hair loss, dry thick skin, and increased sensitivity to cold.

What it does:
ELTROXIN® is given to replace the thyroxine that would normally be produced naturally by the thyroid gland. ELTROXIN®, when taken correctly, reverses the symptoms of hypothyroidism.

Once the thyroid gland becomes unable to produce thyroxine, it will not generally return to normal function. Therefore, once ELTROXIN is started, it usually needs to be taken for the rest of a person's life.

ELTROXIN is also used to treat goiter (enlarged thyroid gland) and congenital hypothyroidism (cretinism).

When it should not be used:
Do not use this medication if:

- If you have had an allergic reaction before to any of the ingredients in ELTROXIN®
- If you have thyrotoxicosis, a disease in which the thyroid gland is overactive and produces too much thyroxine.
- If you have had an acute myocardial infarction (heart attack).
- If you have had uncorrected adrenal insufficiency (kidney problems).

What the medicinal ingredient is:
Levothyroxine sodium

What the important nonmedicinal ingredients are:
Acacia powder, corn starch, lactose, magnesium stearate and coloring agents.

What dosage forms it comes in:
Tablets: 50, 100, 150, 200 and 300 mcg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Thyroid hormones, including ELTROXIN®, either by itself or with other medications should not be used for weight loss. Larger doses may cause serious side effects especially when taken together with medications used for weight loss.

BEFORE you use ELTROXIN® talk to your doctor or pharmacist if:

- you have any other medical problems, especially:
  - Clotting disorders
  - Heart disease
  - A history of problems with your thyroid, adrenal or pituitary gland
  - Diabetes
  - Allergic to any foods or medicines
  - Are pregnant or intend to become pregnant
  - Are breast-feeding, or planning to breast - feed
  - Are taking any other medications, including prescription and over-the-counter medications as well as vitamins and other supplements
  - Are taking medication to thin your blood such as warfarin
  - You are taking orlistat
- Tell your doctor about any surgery you are planning. Before the surgery tell your dentist or surgeon that you are taking ELTROXIN®.

INTERACTIONS WITH THIS MEDICATION

Some medications and foods can interfere with the effectiveness of your thyroid medication or your overall treatment – these are called "drug and food interactions".

Make sure your doctor or healthcare provider has a complete

list of all prescription medications, vitamins, or over-the-counter medications you are currently taking. In some cases, your condition or therapy may need additional monitoring. Your doctor may ask you to take your thyroid medication at a different time of the day, separately from some medications, to avoid potential interactions.

This is not a complete list of drug interactions. For more information, contact your doctor or pharmacist.

Drugs that may interact with ELTROXIN® include:

Nutritional Supplements
- Calcium Carbonate
- Ferrous Sulfate (Iron)

GI Therapies
- Antacids (aluminum and magnesium types)

Cardiovascular Therapies like:
- Digoxin
- Thiazide Diuretics (Hydrochlorothiazide)
- Oral Anticoagulants (Coumadin® - Warfarin Sodium)
- Beta Blockers

Cholesterol Therapies
- Some statins

Antidepressants
- Tricyclics (Amitriptyline)
- Tetracyclics (Maprotiline)
- Reuptake Inhibitors (SSRIs like Prozac® - Fluoxetine)

Other (CNS) Therapies Neurologic/Psychiatric
- Lithium
- Carbamazepine
- Phenobarbital
- Diazepam
- Phenytoin (Dilantin®)

Some Cancer Therapies

General or other Therapies
- Antidiabetic Agents (such as Insulin)
- Oral contraceptive pill
- Drugs used for weight reduction (such as Orlistat)

Drug-Food Interactions
Eating certain foods like soybean flour (infant formula), cotton seed meal, walnuts, calcium and calcium-fortified orange juice, and dietary fibre may decrease absorption of your medicine (levothyroxine sodium).

Please discuss with your doctor whether a dose adjustment of your medicine is necessary.

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dose of ELTROXIN® is different for everyone.

Your doctor will take into account your age, weight, presence of any other illness and the severity and length of time you have been ill prior to beginning treatment with ELTROXIN®.

Overdose:
Symptoms are not always evident or may not appear until several days after taking your ELTROXIN® medication.

Signs and symptoms of overdose include, but are not limited to: weight loss, increased appetite, heart palpitations (fast or irregular beating of heart), nervousness, diarrhea, abdominal cramps, sweating, increased pulse and blood pressure, fever, and menstrual irregularities.

If you suspect that you or anyone else has taken too much ELTROXIN® you may need to seek immediate medical attention.

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

Missed Dose:
Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

ELTROXIN can cause some side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- weight loss, tremor, headache, upset stomach, diarrhea, stomach cramps, nervousness, irritability, insomnia, excessive sweating, increased appetitie, fever, changes in menstrual cycle, sensitivity to heat, temporary hair loss (particularly in children during the first month of therapy)

Seek emergency medical attention or contact your doctor immediately if you experience any of the following:

- an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);
- vomiting; or
- chest pain, irregular heartbeat, shortness of breath.

This is not a complete list of side effects. For any unexpected effects while taking ELTROXIN®, contact your doctor or pharmacist.

HOW TO STORE IT

Store your medication between 15ºC and 25ºC and protect from light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following three ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health care professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found by contacting Aspri Pharma Canada Inc. at 1-855-868-8440 or www.aspripharma.com.

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