

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrELTROXIN®

Levothyroxine sodium

Tablets, 50 mcg, 100 mcg, 150 mcg and 200 mcg, Oral,
BP
Thyroid hormone
ATC Code: H03AA01

Aspen Pharmacare Canada Inc.
201 - 2030 Bristol Circle
Oakville, ON, L6H 0H2

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ELTROXIN® (levothyroxine sodium tablets) is indicated for:

Hypothyroidism

- ELTROXIN® is indicated as a replacement or supplemental therapy in patients of any age with primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism of any etiology, in any state (including pregnancy) except transient hypothyroidism during the recovery phase of subacute thyroiditis.

Pituitary Thyrotropin (Thyroid-stimulating hormone, TSH) Suppression

- ELTROXIN® is indicated as an adjunct to surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ELTROXIN® in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment – Pediatric Dosage).

1.2 Geriatrics

Geriatrics (≥65 years of age): ELTROXIN® is approved for use in the geriatric population. However, dosing precautions apply (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

2 CONTRAINDICATIONS

ELTROXIN® is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section
- Patients with untreated subclinical thyrotoxicosis (suppressed serum TSH with normal L-triiodothyronine/liothyronine [T₃] and L-thyroxine/levothyroxine [T₄] levels) or overt thyrotoxicosis of any etiology.
- Patients with acute myocardial infarction, acute myocarditis and acute pericarditis.
- Patients with uncorrected adrenal insufficiency, as thyroid hormones increase tissue demands for adrenocortical hormones and may thereby precipitate acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see WARNINGS AND PRECAUTIONS).
- Pregnant women with hyperthyroidism treated with anti-thyroid agents. Combination therapy of hyperthyroidism with levothyroxine and anti-thyroid agents is not indicated in pregnancy.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The dosage and frequency of administration of ELTROXIN® is determined by the indication and must in every case be individualized according to patient response and laboratory findings.

Levothyroxine sodium products from different manufacturers should not be used interchangeably unless retesting of the patient and re-titration of the dosage, as necessary, accompanies the product switch.

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 free T₄ (FT₄), 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:

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.

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 ELTROXIN® 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, ELTROXIN® should be given in the smallest dose that will achieve the desired clinical response.

Myxedema Coma: Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral thyroid hormone drug products, such as ELTROXIN®, are not recommended to treat this condition. Thyroid hormone products formulated for intravenous administration should be administered.

Pediatrics – 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 FT_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 1).

4.2 Recommended Dose and Dosage Adjustment Adult Dosage**Adult Dosage****Hypothyroidism**

The usual full replacement dose of ELTROXIN® for adults is approximately 1.7 mcg/kg/day administered once daily. Therapy is usually initiated at the anticipated full replacement dose.

Women who are maintained on levothyroxine sodium during pregnancy may require increased doses (see WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women).

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.

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.

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. Once optimal replacement is achieved, clinical and laboratory evaluations should be conducted at least annually or whenever warranted by a change in patient status.

In older patients or in younger patients with a history of cardiovascular disease, the starting dose should be lower 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.

TSH Suppression in Thyroid Cancer

For well-differentiated thyroid cancer, TSH is generally suppressed to less than 0.1 mU/L. Doses of ELTROXIN® greater than 2 mcg/kg/day are usually required.

ELTROXIN® 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 1). Infants and neonates with very low (<5 mcg/dL) or undetectable serum T₄ levels should be started at the 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, ELTROXIN® 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 T₄ and TSH levels, is achieved.

Table 1: Dosing Guidelines for Pediatric Hypothyroidism

Age	Daily Dose (mcg) per kg of Body Weight ^a
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
>12 years 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 and Special Populations – Pediatrics).

Serum T₄ and TSH measurements should be evaluated at the following intervals, with subsequent dosage adjustments to normalize serum total T₄ or FT₄ and TSH:

- 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 ELTROXIN[®] dose.

4.4 Administration

Administer ELTROXIN[®] as a single daily dose, preferably on an empty stomach, one-half to one-hour before breakfast. As food and drink can significantly change the absorption of levothyroxine sodium, patients should be advised to take levothyroxine sodium at the same time every day and be consistent in how they take it with regards to meals. Administer ELTROXIN[®] at least 4 hours before or after drugs that are known to interfere with its absorption (see DRUG INTERACTIONS).

PEDIATRICS

ELTROXIN[®] 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 (see DRUG INTERACTIONS, Drug-Food Interactions).

4.5 Missed Dose

If a scheduled 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.

5 OVERDOSAGE

Signs and Symptoms

Excessive doses of ELTROXIN® 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, menstrual irregularities, irritability, hyperactivity, headache, mydriasis, tachypnoea, convulsions and seizures. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Symptoms are not always evident or may not appear until several days after ingestion of levothyroxine sodium.

Treatment of Overdosage

ELTROXIN® 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet – 50 mcg, 100 mcg, 150 mcg and 200 mcg of levothyroxine sodium	acacia powder, corn starch, lactose, magnesium stearate and colouring agents(see colouring agents below)

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.

Colouring agents:

- ELTROXIN® Tablets 50 mcg (white) - none
- ELTROXIN® Tablets 100 mcg (yellow) - colorcon yellow
- ELTROXIN® Tablets 150 mcg (blue) - colorcon blue
- ELTROXIN® Tablets 200 mcg (pink) – erythrosine

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

ELTROXIN® 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 ELTROXIN® necessitating adjustments in dosing to maintain therapeutic response (see DRUG INTERACTIONS).

The bioavailability of levothyroxine sodium 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, bioavailability and the excipients in the respective formulation. Therefore, it is recommended that patients who are switched from one levothyroxine sodium formulation to another be re-titrated to the desired thyroid function to avoid the consequences of over- or under-treatment.

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 T₄ 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.

Cardiovascular

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.

ELTROXIN® 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 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, Recommended Dose and Dosage Adjustment).

These patients should be closely monitored during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine sodium. Concomitant administration of thyroid hormone and sympathomimetic agents to patients with coronary artery disease may increase the risk of coronary insufficiency.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

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.

Effects on Bone Mineral Density

In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in postmenopausal women on greater 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 ELTROXIN® 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 sodium 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, ELTROXIN® should be used with caution. In conjunction, there should be careful monitoring of thyroid function for evidence of hyperthyroidism, as well as clinical monitoring for potential cardiovascular signs and also for symptoms of hyperthyroidism.

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).

Myxedema Coma

Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral thyroid hormone drug products, such as ELTROXIN®, are not recommended to treat this condition. Thyroid hormone products formulated for intravenous administration should be administered.

Gastrointestinal

Thyroxine absorption is decreased in patients with malabsorption syndromes. It is advised to treat the malabsorption condition to ensure effective thyroxine treatment with regular thyroxine dose.

Hematologic

T₄ 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.

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. Use of ELTROXIN® 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).

Monitoring and Laboratory Tests

Measurements of FT₄ 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. Treatment of patients with ELTROXIN® 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 (see DRUG INTERACTIONS).

TSH alone may be useful for thyroid disease screening and for monitoring therapy for primary hypothyroidism as a linear inverse correlation exists between serum TSH and FT₄.

Measurement of total serum T₄ and T₃, resin T₃ uptake, and free T₃ 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 T₄ 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 T₄ levels.

Adequacy of levothyroxine sodium therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring FT₄, 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 T₄ or FT₄, which should be maintained in the upper half of the normal range. In congenital hypothyroidism, serum TSH normalization may lag behind serum T₄ normalization by 2 to 3 months or longer. In rare patients, serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal T₄ or FT₄ levels (see WARNINGS AND PRECAUTIONS, Special Populations – Pediatrics).

Serum biotin may interfere with thyroid function immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results (see 9.7 Drug-Laboratory Test Interaction). The risk of interference increases with higher doses of biotin. When possible, it is recommended that patients abstain from taking biotin supplements for at least 2 days prior to specimen collection.

When interpreting results of laboratory tests, possible biotin interference should be taken into consideration, especially if a lack of coherence with the clinical presentation is observed.

Psychiatric

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

Reproductive Health: Female and Male Potential

(See [2 CONTRAINDICATIONS](#) and [7.1.1 Pregnant Women](#)).

- **Fertility**

The use of ELTROXIN® is unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

7.1 Special Populations

7.1.1 Pregnant Women

Studies in pregnant women have not shown that levothyroxine sodium increases the risk of fetal abnormalities if administered during pregnancy.

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. Therefore, ELTROXIN® should not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated.

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.

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 patients taking ELTROXIN® should have their TSH measured approximately every 4 weeks during the first half of pregnancy, and at least once between week 26 and 32, as levothyroxine dose adjustments are often required.

An elevated serum TSH level should be corrected by an increase in the levothyroxine sodium dose. Since postpartum TSH serum levels are similar to preconception values, levothyroxine sodium dosage can be reduced to the pre-pregnancy dose. A serum TSH level should be obtained six to eight weeks postpartum.

7.1.2 Breast-feeding

Adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation. Minimal amounts of thyroid hormones are excreted in human milk; therefore, caution should be exercised when ELTROXIN® is administered to a nursing woman.

7.1.3 Pediatrics

Haemodynamic parameters should be monitored when levothyroxine therapy is initiated in very low birth weight preterm neonates as circulatory collapse may occur due to the immature adrenal function.

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 free T_4 (FT_4) in the upper half of the normal range and serum TSH in the normal range.

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 T₄ or FT₄ levels. Increasing the levothyroxine sodium dosage to suppress TSH into the normal range may produce overtreatment, with an elevated serum T₄ 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

If transient hypothyroidism is suspected hypothyroidism permanence may be assessed after the child reaches 3 years of age. Levothyroxine sodium therapy may be interrupted for 30 days and serum T₄ and TSH measured. Low T₄ and elevated TSH confirm permanent hypothyroidism; therapy should be re-instituted. If T₄ 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 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 ELTROXIN® 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, ELTROXIN® treatment should be discontinued for another 30-day trial period followed by repeat serum T₄ and TSH testing.

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.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Inadequate doses of ELTROXIN® may produce or fail to resolve symptoms of hypothyroidism. Adverse reactions associated with ELTROXIN® are primarily those of hyperthyroidism due to therapeutic overdosage (see WARNINGS AND PRECAUTIONS and OVERDOSAGE). Not all of the

adverse reactions listed below have been observed with ELTROXIN[®], and some have occurred with other levothyroxine sodium formulations.

Table 3: Summary of Adverse Events

System Organ Class	Preferred Term
General disorders and administration site conditions:	fatigue, temperature intolerance, pyrexia
Cardiac disorders:	palpitations, tachycardia, arrhythmias, increased blood pressure, cardiac failure, angina pectoris, myocardial infarction and cardiac arrest
Investigations:	bone density decreased, liver function test increased
Gastrointestinal disorders:	diarrhea, vomiting, abdominal pain, nausea
Immune system disorders:	hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products; these include anaphylactic reaction, 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
Metabolism and nutrition disorders:	increased appetite, abnormal loss of weight
Musculoskeletal and connective tissue disorders:	muscle spasms, muscular weakness; excessive dose may result in craniosynostosis and/or premature closure of epiphyses in children (compromised adult height)
Nervous system disorders:	headache, tremor, seizure. Rare cases of pseudotumor cerebri (benign intracranial hypertension) have been reported especially in children
Psychiatric disorders:	anxiety, affect lability, nervousness, agitation, insomnia, restlessness
Reproductive system and breast disorders:	menstruation irregular, infertility
Respiratory, thoracic and mediastinal disorders:	dyspnoea
Skin and subcutaneous tissue disorders:	hyperhidrosis, alopecia
Vascular disorders:	flushing

9 DRUG INTERACTIONS

9.2 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 agent, 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®.

9.3 Drug-Behavioural Interactions

No drug-behavioural interactions have been established.

9.4 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 ELTROXIN®. 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 4.

The list of drug-thyroidal axis interactions in Table 4 may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Drug-Thyroidal Axis Interactions

Drug or Drug Class	Effect
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: <ul style="list-style-type: none">• 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).

Drug or Drug Class	Effect
Drugs that alter thyroid hormone secretion and/or decrease T₄ 5'-deiodinase activity (conversion of T₄ to T₃) may result in hypothyroidism	
Aminoglutethimide Amiodarone Beta-Adrenergic Antagonists (e.g., propanolol greater than 160 mg/day) Glucocorticoids (e.g., dexamethasone greater than or equal to 4 mg/day) Iodide (including iodine-containing radiographic contrast agents) Lithium Thioamides <ul style="list-style-type: none"> - Methimazole - Propylthiouracil (PTU) - Carbimazole Sulfonamides Tolbutamide	<p>Medicines that (partially) inhibit the peripheral transformation of T₄ to T₃ – like amiodarone, lithium, iodide, oral contrast agents, and propylthiouracil – lower the T₃ level and therefore also the therapeutic effect.</p> <p>In patients treated with large doses of propanolol (greater than 160 mg/day), T₃ and T₄ levels change slightly, TSH levels remain normal, and patients are clinically euthyroid.</p> <p>Actions of some beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state.</p> <p>Short-term administration of large doses of glucocorticoids may decrease serum T₃ concentrations by 30% with minimal change in serum T₄ levels. However, long-term glucocorticoid therapy may result in slightly decreased T₃ and T₄ levels due to decreased TBG production (see above).</p> <p>Refer to below section for effects of amiodarone and iodine in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy.</p>
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy	
Amiodarone Iodide (including iodine-containing radiographic contrast agents)	<p>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).</p> <p>Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.</p>

Drug or Drug Class	Effect
Drugs that may decrease T₄ absorption, which may result in hypothyroidism	
Antacids - Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium carbonate Anion/Cation Exchange Resins - Sevelamer - Kayexalate Ferrous Sulfate Lanthanum Orlistat Polystyrene Sulfonates Proton Pump Inhibitors Sucralfate Supplements - Aluminum Supplements - Magnesium Supplements - Iron Supplements	Concurrent use may reduce the efficacy of levothyroxine sodium by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine sodium, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine sodium at least four (4) hours apart from these agents. Patients treated concomitantly with orlistat and levothyroxine should be monitored for changes in thyroid function.
Drugs that may alter T₄ and T₃ serum transport – but FT₄ concentration remains normal; and therefore, the patient remains euthyroid	
Clofibrate Estrogen-Containing Oral Contraceptives Estrogens (oral) Heroin/Methadone 5-Fluorouracil Mitotane Tamoxifen	Increase in serum TBG concentration, while FT ₄ concentration remains normal.
Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	Decrease in serum TBG concentration, while FT ₄ concentration remains normal.

Drug or Drug Class	Effect
Drugs that may cause protein-binding site replacement	
Furosemide (greater than 80 mg IV) Heparin Hydantoin Non Steroidal Anti-Inflammatory Drugs (NSAIDs) <ul style="list-style-type: none"> - Fenamates - Phenylbutazone - Salicylates (greater than 2 g/day) 	<p>Administration of these agents with levothyroxine sodium results in an initial transient increase in FT₄. Continued administration results in a decrease in serum T₄, while maintaining normal FT₄ and TSH concentrations and, therefore, patients are clinically euthyroid.</p> <p>Salicylates inhibit binding of T₄ and T₃ to TBG and transthyretin. An initial increase in serum T₄ is followed by return of FT₄ to normal levels with sustained therapeutic serum salicylate concentrations, although total-T₄ levels may decrease by as much as 30%.</p>
Drugs that may alter T₄ and T₃ metabolism – drugs that may increase hepatic metabolism, which may result in hypothyroidism	
Carbamazepine Hydantoin Phenobarbital Rifampin Ritonavir	<p>Carbamazepine and Phenytoin reduce serum protein binding of levothyroxine sodium, and total- and FT₄ may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid. Therefore, initiation or discontinuation of anticonvulsant therapy may alter thyroxine sodium dose requirements.</p> <p>Stimulation of hepatic microsomal drug-metabolizing enzyme activity by enzyme inducers such as barbiturates and rifampicin may cause increased hepatic degradation of levothyroxine sodium, resulting in increased levothyroxine sodium requirements.</p> <p>In patients treated concomitantly with ritonavir and levothyroxine, thyroid-stimulating hormone (TSH) should be monitored for at least the first month after starting and/or ending ritonavir treatment.</p>

Drug or Drug Class	Effect
Miscellaneous	
Anticoagulants (oral) <ul style="list-style-type: none"> - Coumarin Derivatives - Indandione Derivatives 	Thyroid hormones increase the anticoagulant activity of oral anticoagulants. Prothrombin time should be carefully monitored in patients taking levothyroxine sodium and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.
Antidepressants <ul style="list-style-type: none"> - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline) 	Concurrent use of tri/tetracyclic antidepressants and levothyroxine sodium may increase the therapeutic and toxic effects of both drugs. 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 sodium may result in increased levothyroxine sodium requirements.
Antidiabetic Agents <ul style="list-style-type: none"> - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - Insulin 	Addition of levothyroxine sodium 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 <ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - 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) <ul style="list-style-type: none"> - 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 $^{99\text{m}}\text{Tc}$.
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 Ciprofloxacin 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.
Tyrosine Kinase Inhibitors <ul style="list-style-type: none"> - Imatinib - Sunitinib 	Concurrent use has been associated with increased thyroxine dosage requirements in hypothyroid patients.

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

St. John's Wort may increase hepatic metabolism of levothyroxine, which may result in hypothyroidism.

9.7 Drug-Laboratory Test Interactions

A number of drugs and foods 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.

Changes in Thyroxine-Binding Globulin (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.

Serum biotin may interfere with thyroid function immunoassays that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results (see [7 WARNINGS AND PRECAUTIONS](#), Monitoring and Laboratory Tests). When available, alternative tests not susceptible to biotin interference should be used for patients taking biotin-containing products.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ELTROXIN® contains levothyroxine sodium, which is the synthetic form of the hormone thyroxine (T_4) produced by the thyroid gland.

The synthesis and secretion of the major thyroid hormones, T_4 and 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.

10.3 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. T₄ 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). T₄ is more extensively and firmly bound to serum proteins than is T₃. Only unbound thyroid hormone is metabolically active. The higher affinity of TBG and TBPA for T₄ 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 Tests and DRUG INTERACTIONS).

Metabolism:

The liver is the major site of degradation for both hormones. T₄ and T₃ 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. About 70 percent of the T₄ secreted daily is deiodinated to yield equal amounts of T₃ and reverse triiodothyronine (rT₃). Subsequent deiodination of T₃ and rT₃ yields multiple forms of diiodothyronine. A number of other minor T₄ metabolites have also been identified. Although some of these metabolites have biologic activity, their overall contribution to the therapeutic effect of T₄ is minimal.

Elimination:

Thyroid hormones are primarily eliminated by the kidneys. In man, approximately 30 to 55% of a dose of thyroxine is excreted in the urine and approximately 20 to 40% of thyroxine is eliminated in the faeces.

T₄ is eliminated slowly from the body (see Table 5), with a half-life of 6 to 7 days in a normal person. This may be reduced in hyperthyroid states or increased in hypothyroid patients. T₃ has a half-life of 1 to 2 days.

Table 5: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	t _{1/2} (days)	Protein Binding(%) ²
Levothyroxine, T ₄	10 to 20	14	6 to 7 ¹	99.96

¹ Three to four days in hyperthyroidism, nine to ten days in hypothyroidism

² Includes TBG, TBPA, and TBA

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 25°C. Protect from light. Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

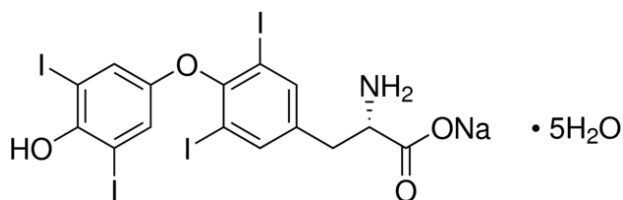
Drug Substance

Proper name: levothyroxine sodium

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

Molecular formula and molecular mass: $C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$ and 888.852 g/mol (pentahydrate); 798.86 (anhydrous)

Structural formula:



Physicochemical properties: Levothyroxine sodium pentahydrate 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.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether ELTROXIN[®] affects fertility in males or females.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ELTROXIN®
Levothyroxine Sodium Tablets

Read this carefully before you start taking **ELTROXIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ELTROXIN**.

Serious Warnings and Precautions

Thyroid hormones, including ELTROXIN, either alone or with other medicines, should not be used for the treatment of obesity or for weight loss. If used for these conditions, it could cause serious or even life-threatening side effects

What is ELTROXIN used for?

- To treat hypothyroidism. This condition happens when the thyroid gland does not produce enough of the hormone thyroxine
- To treat certain types of thyroid cancer. For these patients, ELTROXIN is given in combination with surgery and radioactive iodine therapy.

How does ELTROXIN work?

ELTROXIN contains levothyroxine sodium which is the synthetic (man-made) form of thyroxine. Thyroxine is a hormone normally produced by the thyroid gland. It helps the body to function properly.

Hypothyroidism occurs when the thyroid gland is unable to produce normal amounts of thyroxine. ELTROXIN treats the symptoms of hypothyroidism by helping to normalize the levels of thyroid hormones in the body.

What are the ingredients in ELTROXIN?

Medicinal ingredients: levothyroxine sodium

Non-medicinal ingredients: acacia powder, colorcon blue (150 mcg), colorcon yellow (100 mcg), corn starch, erythrosine (200 mcg), lactose, and magnesium stearate.

ELTROXIN comes in the following dosage forms:

Tablets: 50 mcg, 100 mcg, 150 mcg and 200 mcg of levothyroxine sodium

Do not use ELTROXIN if:

- are allergic (hypersensitive) to levothyroxine sodium or to any of the other ingredients in ELTROXIN
- have thyrotoxicosis, a disease in which the thyroid gland is overactive and produces too much thyroxine
- have had a heart attack, inflammation of the heart muscles or other serious heart problem
- have a condition where your kidneys do not make enough of the hormone cortisol (uncorrected adrenal insufficiency)
- you are pregnant and are taking medication to treat hyperthyroidism (overactive thyroid)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ELTROXIN. Talk about any health conditions or problems you may have, including if you:

- have any clotting disorders or are taking medication to thin your blood such as warfarin
- have heart problems
- have high blood pressure
- have a history of problems with your thyroid, adrenal or pituitary gland
- have diabetes or another autoimmune disorder
- have trouble absorbing nutrients from your gut (malabsorption syndrome)
- are switching from a different brand of levothyroxine;
- are pregnant or intend to become pregnant. Your healthcare professional may examine your blood during your pregnancy to measure the amount of THS (Thyroid Stimulating Hormone)
- are breast-feeding, or planning to breast-feed
- are 65 years of age or older
- have psychiatric disorders. Your healthcare professional may start your treatment of ELTROXIN at a lower dosage.

Other warnings you should know about:**Surgery:**

Tell your healthcare professional about any surgery you are planning to have. Before the surgery tell your dentist or surgeon that you are taking ELTROXIN.

Monitoring and blood tests

Taking a biotin supplement may affect blood tests done to check thyroid hormone levels (called thyroid function tests). Tell your healthcare professional if you are taking biotin. It may lead to false test results. Your healthcare professional may ask you to stop taking biotin at least 2 days before you have a thyroid function test.

Driving and Operating Machinery

While taking ELTROXIN, use caution when driving or operating potentially dangerous machinery.

Myxedema coma

Oral thyroid hormone medications, including ELTROXIN, are not recommended to treat myxedema coma. Myxedema coma is a severe hypothyroid condition that may cause irregular absorption of ELTROXIN. Thyroid hormone medications taken intravenously (through the vein) should be used instead of oral (by mouth) thyroid hormone medications.

Premature babies with very low birth weight: Blood pressure may be monitored regularly when levothyroxine treatment is started. This is because levothyroxine can cause a fast drop in blood pressure (known as circulatory collapse).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ELTROXIN:

- Nutritional Supplements
 - Biotin (vitamin B7, vitamin H; including for hair and nail)
 - Calcium carbonate
 - Ferrous sulfate (iron)
- Medicines used to treat digestion problems
 - Antacids (aluminum and magnesium types)
 - Simethicone
 - Proton-pump inhibitors
 - Sucralfate
- Medicines used to treat heart problems including high blood pressure
 - Digoxin
 - Amiodarone
 - Thiazide diuretics (hydrochlorothiazide)
 - Oral anticoagulants (warfarin sodium)
 - Beta blockers
- Medicines used to lower high cholesterol
 - Some statins (like lovastatin, simvastatin)
 - Cholestyramine
 - Colestipol
 - Clofibrate
- Medicines used to treat depression (antidepressants)
 - St John's Wort
 - Tricyclics (amitriptyline)
 - Tetracyclics (maprotiline)
 - Reuptake inhibitors (SSRIs like fluoxetine, sertraline)
- Medicines used to other treat mental health problems and seizures
 - Lithium
 - Carbamazepine
 - Phenobarbital
 - Diazepam
 - Phenytoin

- Methadone
- Medicines used to treat diabetes
 - Insulin
 - Tolbutamine
 - Biguanides
 - Meglitinides
 - Sulfonylureas
 - Thiazolidinediones
- Hormones
 - Birth control pills
 - Hormone replacement therapy
 - Testosterone
 - Growth hormones (like somatrem, somatropin)
- Some cancer therapies
- Medicines used for weight reduction
 - Orlistat
- Medicines used to treat inflammatory conditions
 - Dexamethasone
 - Prednisone
 - Hydrocortisone
- Medicines used to treat bacterial infections
 - Sulfonamides
 - Rifampin
 - Ciprofloxacin
- Medicines used to treat Human immunodeficiency viruses (HIV)
 - Ritonavir
- Medicines used to treat kidney problems
 - Sevelamer
 - Kayexalate
 - Lanthanum
- Medicines used to treat high levels of potassium in the blood (hyperkalemia)
 - Polystyrene sulfonates
- Other medicines used to treat thyroid problems
 - Methimazole
 - Propylthiouracil (PTU)
 - Carbimazole
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
 - Fenamates
 - Phenylbutazone
 - Salicylates
- Oral contrast agents used in imaging like x-rays and CT scans
 - Iodide
- 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 cause less ELTROXIN to be absorbed.

How to take ELTROXIN:

Your healthcare professional will tell you how and when to take ELTROXIN. They may ask you to take ELTROXIN at a different time of the day, separately from other medications, to avoid potential drug interactions.

Take ELTROXIN once a day. It is recommended you take ELTROXIN:

- on an empty stomach;
- 30 minutes to one hour before breakfast;
- at least 4 hours before or after you take medications that can impact the absorption of ELTROXIN.

For infants and children who cannot swallow ELTROXIN, the tablets can be crushed and added to a small amount (5 to 10 mL) of water, breast milk or non-soybean based formula.

The tablet and liquid mixture can be given by spoon or dropper. **If the tablet and liquid mixture is not consumed immediately it must be thrown out.**

ELTROXIN tablets can also be crushed and sprinkled over a small amount of food such as apple sauce. Do **not** add the crushed tablets to foods containing large amounts of soybean, fiber, or iron. **If the tablet and food mixture is not consumed immediately it must be thrown out.**

Usual Dose:

The usual dose of ELTROXIN is different for everyone.

Your healthcare professional will decide on the dose that is right for you based on your age, your weight, if you have any other illness and how long you were sick before beginning treatment with ELTROXIN.

Overdose:

Symptoms may not appear until several days after taking too much ELTROXIN.

Signs and symptoms of overdose may include: weight loss, increased appetite, heart palpitations (fast or irregular beating of the heart), nervousness, diarrhea, abdominal cramps, sweating, fast heartbeat, fever, menstrual irregularities, convulsions and seizures (fits) and in some cases coma and death.

If you think you, or a person you are caring for, have taken too much ELTROXIN, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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. If you miss more than two doses, contact your healthcare professional.

What are possible side effects from using ELTROXIN?

These are not all the possible side effects you may have when taking ELTROXIN. If you experience any side effects not listed here, tell your healthcare professional.

- changes in menstrual cycle
- diarrhea, nausea, vomiting, stomach cramps
- fatigue, sleepiness
- fever
- headache
- heat intolerance, flushing, excessive sweating
- infertility
- muscle spasms and/or weakness, tremors
- reduced adult height in children due to early closure of growth plates in bones
- restlessness, anxiety, nervousness, agitation, rapid changes in emotions
- temporary hair loss (particularly in children during the first month of therapy)
- trouble sleeping (insomnia)

ELTROXIN can cause abnormal test results. Your healthcare professional will decide when to perform blood tests and other diagnostic tests and will interpret the results.

Serious Side Effects and What To Do About Them			
Symptom / Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Unknown			
Heart Problems: chest pain, rapid or irregular heartbeat, palpitations, shortness of breath			√
Heart Attack: crushing chest pain that radiates to the left arm and/or jaw, sweating, nausea, vomiting, shortness of breath			√
Heart Failure: shortness of breath when you exert yourself or lie down, fatigue, weakness, swelling in the legs, ankles and feet, rapid or irregular heartbeat, persistent cough			√
Serious Allergic Reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Seizures (fits)			√
Change in appetite, weight gain or loss	√		
Increased Pressure in the Brain (in children): headaches, vision problems or complete vision loss, seeing double, ringing in the ears, pain in the arms			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

Store ELTROXIN at room temperature (15°C to 25°C) and protect from light. Keep out of reach and sight of children.

If you want more information about ELTROXIN.

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website: <https://aspenpharma.ca> or by calling 1 (844) 330-1213.

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Aspen Pharmacare Canada Inc.
201 - 2030 Bristol Circle
Oakville, ON, L6H 0H2

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