PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] LEVOTHYROXINE SODIUM FOR INJECTION

Levothyroxine Sodium for Injection

Powder for Solution

200 mcg / vial and 500 mcg / vial

Intravenous or Intramuscular

Thyroid Hormone

ATC Code: H03AA01

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	03/2022
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LEVOTHYROXINE SODIUM FOR INJECTION (levothyroxine sodium for injection) is indicated for:

- the treatment of overt hypothyroidism of any etiology when parenteral use is clinically warranted, such as when rapid repletion is required, or when oral administration is precluded.

1.1 Pediatrics

Pediatrics: LEVOTHYROXINE SODIUM FOR INJECTION is approved for use in the pediatric population. However, dosing and monitoring considerations apply (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Pediatric Dosage).

1.2 Geriatrics

Geriatrics: LEVOTHYROXINE SODIUM FOR INJECTION is approved for use in the geriatric population. However, dosing precautions apply (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Geriatric Dosage).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with untreated subclinical [suppressed serum TSH level with normal triiodothyronine (T_3) and levothyroxine (T_4) levels] or overt thyrotoxicosis of any etiology.
- Patients with acute myocardial infarction, acute myocarditis, or acute pancarditis.
- Patients with uncorrected/untreated adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see 7 WARNINGS AND PRECAUTIONS, Immune, Autoimmune Polyglandular Syndrome).
- Pregnant women with hyperthyroidism treated with antithyroid agents. Combination therapy of hyperthyroidism with levothyroxine and antithyroid agents is not indicated in pregnancy (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Thyroid hormones, including levothyroxine, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

LEVOTHYROXINE SODIUM FOR INJECTION can be used intravenously or intramuscularly in place of the oral dosage form when oral administration is precluded.

LEVOTHYROXINE SODIUM FOR INJECTION can be used intravenously in place of the oral dosage form when rapid repletion is required.

The relative bioavailability between LEVOTHYROXINE SODIUM FOR INJECTION and oral levothyroxine products has not been established. Based on medical practice, the relative bioavailability between oral and intravenous administration of LEVOTHYROXINE SODIUM FOR INJECTION is estimated to be from 48 to 74%. Caution should be used when switching patients from oral levothyroxine products to LEVOTHYROXINE SODIUM FOR INJECTION as accurate dosing conversion has not been studied.

LEVOTHYROXINE SODIUM FOR INJECTION should be administered, as clinically indicated, until the patient can tolerate oral therapy and is clinically stable. For chronic treatment of hypothyroidism, an oral dosage form of levothyroxine should be used to maintain a euthyroid state.

Due to differences in absorption characteristics of patients and the oral levothyroxine product formulations, TSH and thyroid hormone levels should be measured a few weeks after initiating oral levothyroxine and dose adjusted accordingly until the serum TSH concentration is normalized and signs and symptoms resolve (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

4.2 Recommended Dose and Dosage Adjustment

Use of LEVOTHYROXINE SODIUM FOR INJECTION in place of the oral dosage form when oral administration is precluded: Based on medical practice, the initial parenteral dosage should be between 48 to 74% of the previously established oral dosage form of levothyroxine sodium tablets.

If cardiac symptoms develop or worsen, the cardiac disease should be evaluated and the dose of LEVOTHYROXINE SODIUM FOR INJECTION reduced (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). Rarely, worsening angina or other signs of cardiac ischemia may prevent achieving a TSH in the normal range.

Daily administration of LEVOTHYROXINE SODIUM FOR INJECTION should be maintained until the patient is capable of tolerating an oral dose and is clinically stable. For chronic treatment of hypothyroidism, an oral dosage form of levothyroxine should be used to maintain a euthyroid state.

Intravenous Use of LEVOTHYROXINE SODIUM FOR INJECTION, When Rapid Repletion is Required e.g., Myxedema Coma: An initial intravenous loading dose of LEVOTHYROXINE SODIUM FOR INJECTION, usually between 300 to 500 mcg, is given to replete the peripheral pool of T_4. The initial dose is followed by daily intravenous doses of 50 to 100 mcg until the patient is stable and oral administration is feasible. Normal T_4 levels are usually achieved in 24 hours, followed by progressive increases in T_3. Improvement in cardiac output, blood pressure, temperature, and mental status generally occur within 24 hours, with improvement in many manifestations of hypothyroidism in 4 to 7 days.

Dosing in Pediatrics: Myxedema coma is a disease of the elderly. An approved oral dosage form of levothyroxine should be used in the pediatric patient population for maintaining a euthyroid state in non-complicated hypothyroidism. The initial parenteral dosage should be approximately one-half the previously established oral dosage of levothyroxine sodium tablets.

Dosing in the Elderly and in Patients with Cardiovascular Disease: Intravenous levothyroxine may be associated with cardiac toxicity, including arrhythmias, tachycardia, myocardial ischemia and infarction, or worsening of congestive heart failure and death in the elderly and in those with underlying cardiovascular disease. In the elderly, the full replacement dose may be altered by decreases in T_4 metabolism. Therefore, cautious use, including doses in the lower end of the recommended range, may be warranted in these populations.

4.3 Reconstitution

Reconstitute the lyophilized Levothyroxine Sodium for Injection by aseptically adding 5 mL of 0.9% Sodium Chloride Injection, USP only.

Do not use Bacteriostatic Sodium Chloride Injection, USP, as the bacteriostatic agent may interfere with complete reconstitution.

Shake vial to ensure complete mixing. Use immediately after reconstitution.

The resultant solution will have a final concentration of approximately 40 mcg per mL and 100 mcg per mL for the 200 mcg and 500 mcg vials, respectively.

4.4 Administration

LEVOTHYROXINE SODIUM FOR INJECTION can be used intravenously in place of the oral dosage form when rapid repletion is required. It can also be used intravenously or intramuscularly when oral administration is precluded.

Administration of LEVOTHYROXINE SODIUM FOR INJECTION by the subcutaneous route is not recommended as studies have shown that the influx of T_4 from the subcutaneous site is very slow, and depends on many factors such as volume of injection, the anatomic site of injection, ambient temperature, and presence of vasospasm.

Do not add LEVOTHYROXINE SODIUM FOR INJECTION to other IV fluids.

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

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

Caution should be exercised when administering LEVOTHYROXINE SODIUM FOR INJECTION to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

4.5 Missed Dose

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

5 OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism (see 8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview). Overdose may cause symptoms of a significant increase in the metabolic rate. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Levothyroxine overdose may also lead to symptoms of acute psychosis, especially in patients at risk of psychotic disorders. Symptoms may appear several days after the overdose of levothyroxine sodium. Several cases of sudden cardiac death have also been reported in patients with many years of levothyroxine sodium abuse.

An elevated T_3 level is a reliable indicator of overdose, more so than elevated T_4 or free T_4 (FT_4) levels.

Depending on the extent of the overdose it is recommended that treatment with LEVOTHYROXINE SODIUM FOR INJECTION is stopped, and that thyroid hormone monitored.

For management of a suspected drug overdose, contact your regional poison control centre.

Acute Massive Overdosage: This may be a life-threatening emergency; therefore, symptomatic and supportive therapy should be instituted immediately. Beta-sympathomimetic effects or increased central and peripheral sympathetic activity such as tachycardia, anxiety, agitation or hyperkinesia may be treated by administering betablockers, e.g., propranolol, provided that there are no medical contraindications to their use. Provide respiratory support as needed; control congestive heart failure and arrhythmia; control fever, hypoglycemia, and fluid loss as necessary. Large doses of antithyroid drugs (e.g., methimazole or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones. Glucocorticoids may be given to inhibit the conversion of T_4 to T_3. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Due to its high protein binding, levothyroxine sodium cannot be eliminated via hemodialysis or hemoperfusion.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Injection (intravenous or intramuscular)	Lyophilized **Powder for solution** 200 mcg / vial 500 mcg / vial	Dibasic sodium phosphate heptahydrate, mannitol and sodium hydroxide.

LEVOTHYROXINE SODIUM FOR INJECTION: Sterile lyophilized powder for reconstitution is supplied in 10 mL single-dose vials:

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

The stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see the 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

Levothyroxine has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or undertreatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism.

Many drugs interact with levothyroxine sodium, necessitating adjustments in dosing to maintain therapeutic response (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).

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

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

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

Carcinogenesis and Mutagenesis

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

Cardiovascular

Excessive bolus dosing of LEVOTHYROXINE SODIUM FOR INJECTION (greater than 500 mcg) are associated with cardiac complications, particularly in the elderly and in patients with an underlying cardiac condition.

Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility, and may precipitate angina or arrhythmias. Close observation of the patient following the administration of LEVOTHYROXINE SODIUM FOR INJECTION is advised.

If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency. Hence, frequent checks of thyroid hormone parameters must be performed in these cases.

Exercise caution when administering LEVOTHYROXINE SODIUM FOR INJECTION to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosing in the Elderly).

Endocrine and Metabolism

Hypothalamic/Pituitary Hormone Deficiencies: In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered and, if diagnosed, treated for adrenal insufficiency (see 7 WARNINGS AND PRECAUTIONS, Immune, Autoimmune Polyglandular Syndrome).

Bone Mineral Density: Supra-physiological serum levels of levothyroxine sodium should be avoided in postmenopausal women with hypothyroidism and an increased risk of osteoporosis. Close monitoring of the thyroid function is recommended. It is recommended that these patients should be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Hematologic

T_4 enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both levothyroxine and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).

Immune

Autoimmune Polyglandular Syndrome: Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with LEVOTHYROXINE SODIUM FOR INJECTION. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with levothyroxine (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).

Monitoring and Laboratory Tests

Clinical and laboratory evaluations should generally be performed at 6 to 8 week intervals (2 to 4 weeks in severely hypothyroid patients), and the dosage adjusted, if necessary, until the serum TSH concentration is normalized and signs and symptoms resolved.

Adequacy of levothyroxine sodium therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring FT_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.

Psychiatric

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

Reproductive Health: Female and Male Potential

Fertility: LEVOTHYROXINE SODIUM FOR INJECTION should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism. Animal studies have not been performed to evaluate the effects of levothyroxine on fertility.

Teratogenic Risk: Studies in pregnant women treated with oral levothyroxine to maintain a euthyroid state have not shown an increased risk of congenital abnormalities.

7.1 Special Populations

7.1.1 Pregnant Women

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development.

Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent *in utero* hypothyroidism.

Combination therapy of LEVOTHYROXINE SODIUM FOR INJECTION and an antithyroid agent for hyperthyroidism is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). Such combination would require higher doses of anti-thyroid agents, which are known to pass the placenta and to induce hypothyroidism in the infant.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

An approved, oral dosage form of levothyroxine should be used in the pediatric patient population for maintaining an euthyroid state in non-complicated hypothyroidism.

7.1.4 Geriatrics

In the elderly, the full replacement dose may be altered by decreases in T_4 metabolism. Furthermore, there is increased prevalence of cardiovascular disease, with atrial fibrillation being a common side effect associated with levothyroxine treatment in the elderly. Therefore, cautious use, including doses in the lower end of the recommended range, may be warranted in these populations (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Dosing in the Elderly).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage. Adverse reactions observed with levothyroxine use include the following:

Cardiac Disorders:	palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, cardiac failure, angina, myocardial infarction and cardiac arrest
Gastrointestinal System:	diarrhea, vomiting, abdominal cramps
General:	fatigue, heat intolerance, fever, excessive sweating, exophthalmic goiter, pseudotumor cerebri (in children)
Immune System Disorders:	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.
Investigations:	decreased bone mineral density; elevations in liver function tests
Metabolism and Nutrition Disorders:	increased appetite, weight loss
Musculoskeletal and Connective Tissue:	tremors, muscle weakness, muscle spasm; slipped capital femoral epiphysis in children, excessive dose may result in premature closure of the epiphyses in children (with resultant compromised adult height)
Nervous System:	headache, pseudotumour cerebri, seizures
Psychiatric Disorders:	anxiety, emotional lability, hyperactivity, insomnia, irritability, nervousness and restlessness,
Reproductive System:	menstrual irregularities, impaired fertility
Respiratory System:	dyspnea
Skin and subcutaneous tissue disorders:	alopecia (generally transient), flushing, rash
Vascular Disorders:	flushing

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.4 Drug-Drug Interactions

The list of drug-thyroidal axis interactions in Table 1 may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions.

Table 1: Established or Potential Drug-Drug Interactions

Drug or Drug Class	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: • 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 aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. 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. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto'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.

Drug or Drug Class	Effect
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing radiographic contrast agents)	Amiodarone may induce hyperthyroidism by causing thyroiditis. Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Graves' disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation.
Drugs that may alter T_4 and T_3 serum transport – but FT_4 concentration remains normal; and therefore, the patient remains euthyroid	
Clofibrate Estrogen-containing Oral Contraceptives Estrogens (oral) Heroin/Methadone 5-Fluorouracil Mitotane Tamoxifen	Increase serum TBG Concentration
Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	Decrease serum TBG Concentration
Drugs that may cause protein-binding site displacement	
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 sodium results in an initial transient increase in FT_4. Continued administration results in a decrease in Serum T_4 and normal FT_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total-T_4 levels may decrease by as much as 30%.

Drug or Drug Class	Effect
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	Phenytoin and carbamazepine reduce serum protein binding of levothyroxine sodium, and total and FT_4 may be reduced by 20 to 40%, but most patients have normal serum TSH levels and are clinically euthyroid. Stimulation of hepatic microsomal drug-metabolizing enzyme activity such as rifampicin and barbiturates may cause increased hepatic degradation of levothyroxine sodium, resulting in increased levothyroxine sodium requirements. Post marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine, resulting in TSH increased levels and hypothyroidism. TSH should be monitored in patients treated concomintantly with ritonavir and levothyroxine for at least the first month after starting and/or ending ritonavir treatment.
Drugs that may decrease T_4 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists - (e.g., Propranolol 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 propranolol (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 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).

Drug or Drug Class	Effect
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 sodium 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 sodium 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 sodium may result in increased levothyroxine sodium requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidediones - 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 - 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.
Growth Hormones - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.

Drug or Drug Class	Effect
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.
Tyrosine Kinase Inhibitors	Plasma concentration of levothyroxine (thyroxine) possibly reduced by Tyrosine Kinase Inhibitors (e.g. imatinib, sunitinib).
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Raloxifen Thiazide Diuretics	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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

Changes in Thyroid-Binding Globule (TBG) concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free-T_4 index (FT_4I). Pregnancy, infectious hepatitis, estrogens, estrogen-

containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or glucocorticoid therapy (see Table 1). Familial hyper or hypo thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Thyroid hormones exert their physiologic actions through control of DNA transcription and protein synthesis. T_3 and T_4 diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. Changes in protein concentrations are responsible for the metabolic changes observed in organs and tissues.

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

10.2 Pharmacodynamics

LEVOTHYROXINE SODIUM FOR INJECTION (levothyroxine sodium for injection) contains synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T_4 is identical to that produced in the human thyroid gland.

Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development. Thyroid hormones also appear to have direct effects on tissues, such as increased myocardial contractility and decreased systemic vascular resistance.

10.3 Pharmacokinetics

Absorption

Following intravenous administration of levothyroxine sodium for injection, the synthetic levothyroxine cannot be distinguished from the natural hormone that is secreted endogenously. Absorption following intramuscular administration is variable.

Distribution

Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding pre-albumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to T_3. Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions and 9.7 Drug-Laboratory Test Interactions). Thyroid hormones do not readily cross the placental barrier (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Metabolism

The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T_3 is derived from peripheral T_4 by monodeiodination 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. T_3 and rT_3 are further deiodinated to diiodothyronine. The liver is the major site of degradation for both T_4 and T_3, with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination

Thyroid hormones are primarily eliminated by the kidneys. T_4 is slowly eliminated (see Table 2).

A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

Table 2: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{½}$ (days)	Protein Binding (%)[2]
Levothyroxine (T_4)	10-20	1	6-7[1]	99.96
Liothyronine (T_3)	1	4	≤ 2	99.5

[1] 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism
[2] Includes TBG, TBPA, and TBA

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature between 15 and 30°C, protected from light.

Single-dose vial. Use immediately after reconstitution. The reconstituted drug product is stable for a period of 4 hours at 25°C. Discard any unused portion. Keep in a safe place out of the sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

The information is not available for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

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

Proper name: Sodium Levothyroxine ($L\text{-}T_4$, Na)

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

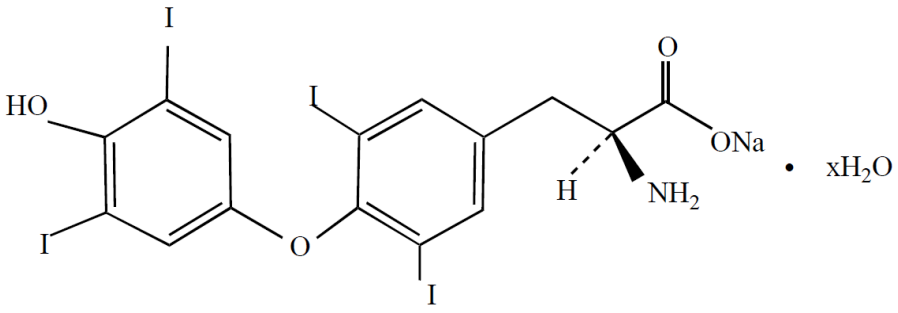
(2) Monosodium L-thyroxine hydrate

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

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

798.85 g/mol (anhydrous)

Structural formula:



Product Characteristics

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

Solubility: Very slightly soluble in water

Slightly soluble in ethanol

Soluble in alkali hydroxide solutions

Solvent	g/100 mL
H2O	0.14
95% ethanol	0.3, 0.4
alkali hydroxides	soluble
chloroform	almost insoluble
ethyl ether	almost insoluble
pH 7.4 buffer	0.022 - 0.044

Melting point:

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

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

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

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

14 CLINICAL TRIALS

No clinical studies have been conducted with levothyroxine sodium for injection.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Animal studies have not been performed to evaluate the toxicology, carcinogenic potential, mutagenic potential or effects on fertility of levothyroxine sodium for injection.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Euthyrox®, levothyroxine sodium, tablets, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg, submission control no. 184137, Product Monograph, EMD Serono, August 6, 2015.
2. Synthroid®, levothyroxine sodium, tablets, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg, submission control no 238350, Product Monograph, BGP Pharma ULC, September 17, 2020.
3. Tirocap™, levothyroxine sodium, capsules, 13 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg, submission control no. 248553, Product Monograph, Institut Biochimique SA (IBSA), June 17, 2021.
4. Levothyroxine Sodium for Injection, levothyroxine sodium, powder, 200 mcg/vial and 500 mcg/vial and Levothyroxine Sodium Injection, levothyroxine sodium, solution, 200 mcg/5 mL (40 mcg/mL) and 500 mcg/5 ml (100 mcg/mL), submission control no. 246606, Product Monograph, Fresenius Kabi Canada Ltd., July 28, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] LEVOTHYROXINE SODIUM FOR INJECTION

Levothyroxine Sodium for Injection (powder for solution)

Read this carefully before you start taking **LEVOTHYROXINE SODIUM FOR INJECTION** 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 **LEVOTHYROXINE SODIUM FOR INJECTION**.

Serious Warnings and Precautions

- Thyroid hormones, including levothyroxine, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss.
- These medicines can cause serious or life-threatening side effects.

What is LEVOTHYROXINE SODIUM FOR INJECTION used for?

- To treat hypothyroidism
- When rapid treatment is required or when oral medication cannot be taken.

How does LEVOTHYROXINE SODIUM FOR INJECTION work?

Levothyroxine is a synthetic (man-made) thyroid hormone. It is intended to replace the hormone thyroxine, produced by a normally functioning thyroid gland. In hypothyroidism, the thyroid gland does not produce enough thyroxine. This causes levels of thyroid hormones in the blood to drop. LEVOTHYROXINE SODIUM FOR INJECTION helps to replace or supplement thyroxine in the body when tablets or capsules cannot be used.

What are the ingredients in LEVOTHYROXINE SODIUM FOR INJECTION?

Medicinal ingredient: Levothyroxine sodium

Non-medicinal ingredients: Dibasic sodium phosphate heptahydrate, mannitol and sodium hydroxide.

LEVOTHYROXINE SODIUM FOR INJECTION comes in the following dosage forms:

- powder for solution; 200 mcg / vial
- powder for solution; 500 mcg / vial

Do not use LEVOTHYROXINE SODIUM FOR INJECTION if:

- you have an overactive thyroid gland;
- you have uncorrected or untreated adrenal insufficiency. This is a condition where your adrenal glands do not make enough of the hormone cortisol;
- you have recently had a heart attack;
- you are pregnant and taking medicines to treat an overactive thyroid;

- you are allergic to any of the ingredients in LEVOTHYROXINE SODIUM FOR INJECTION.

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

- are allergic to any foods or medicines;
- have any heart problems and whether or not you received treatment for them. This includes:
    - hardening of the arteries
    - angina
    - irregular heartbeat
    - heart failure
    - heart disease;
- have any other medicinal problems and whether or not you have received treatment for them. This includes:
    - high blood pressure
    - osteoporosis
    - blood clotting disorders
    - history of thyroid, adrenal, or pituitary gland problems;
- are taking blood thinners such as warfarin. Your dose may need to be changed after starting LEVOTHYROXINE SODIUM FOR INJECTION;
- have signs or symptoms of psychotic disorders;
- are a woman on long term levothyroxine treatment. This is because you may experience bone loss. This is also known as lowered bone mineral density;
- are or intend to become pregnant;
- are 65 years of age or older.

Other warnings you should know about:

Diabetes or adrenal insufficiency: If you are receiving treatment for these conditions, the doses of those treatments may need to be changed after starting LEVOTHYROXINE SODIUM FOR INJECTION. Monitor sugar levels in your blood and urine as directed by your doctor. Report any changes to your doctor right away.

Breast-feeding: Small amounts of thyroid hormones will pass into your breast milk. Your treatment with LEVOTHYROXINE SODIUM FOR INJECTION may continue while you are breast- feeding.

Blood tests: You will need to have regular blood tests while you are receiving LEVOTHYROXINE SODIUM FOR INJECTION. These will be done to make sure that you are receiving the correct dose. As well, the results of these tests will help your doctor to know how your treatment is affecting your blood.

Surgery: Tell your healthcare professional about any surgery (including dental surgery) you are planning. Before the surgery, tell your doctor or dentist that you are receiving LEVOTHYROXINE SODIUM FOR INJECTION.

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 LEVOTHYROXINE SODIUM FOR INJECTION:

- Medicines used to treat heart problems including high blood pressure such as:
    - digitalis glycosides (e.g., digoxin)
    - beta-adrenergic antagonists, also called beta-blockers (e.g., metoprolol, atenolol, bisoprolol, propranolol)
    - blood thinners such as warfarin, dicumarol and coumarin derivatives,
    - amiodarone
    - diuretics like furosemide
- Medicines used to treat diabetes including insulin and other medicines used to lower blood sugar levels.
- Medicines used to treat bacterial infections such as sulfonamides.
- Medicines used to treat inflammatory conditions such as:
    - glucocorticoids (corticosteroids)
    - salicylates
- Medicines used to lower high cholesterol such as clofibrate.
- Medicines used to treat mental health problems and seizures such as:
    - diazepam
    - antidepressants like amitriptyline, maprotiline and sertraline
    - lithium
    - phenytoin
    - barbiturates
    - carbamazepine
- Iodide, which is used for imaging like x-rays and CT scans.
- Hormones such as estrogens that are taken by mouth including birth control.
- Medicines used to treat types of cancer such as tyrosine kinase inhibitors.
- Medicines used anesthesia such as ketamine.
- Beta-sympatholytics/sympathomimetics, which are used to stimulate the heart and treat breathing problems.
- Other medicines used to treat thyroid problems such as:
    - propylthiouracil (PTU)
    - methimazole

How LEVOTHYROXINE SODIUM FOR INJECTION is given:

LEVOTHYROXINE SODIUM FOR INJECTION powder will be first mixed into a solution.

- LEVOTHYROXINE SODIUM FOR INJECTION will be given to you by a healthcare professional.
- Your healthcare professional will check the solution to make sure it is not cloudy or leaking.
- The solution of LEVOTHYROXINE SODIUM FOR INJECTION will then be given through a needle placed in a vein in your arm. This is called an intravenous (IV) injection. It may also be given through an injection in your muscle. This is called an intramuscular (IM) injection.
- Any unused portion will be discarded.

Usual dose:

The usual dose of LEVOTHYROXINE SODIUM FOR INJECTION will be different for everyone. Your healthcare professional will decide on the dose that is right for you. Your dose will depend on:

- your age,
- your weight,
- other conditions or illnesses you have, including any heart problems,
- how long you had symptoms of thyroid problems, and
- how severe your symptoms are.

Overdose:

You may not experience symptoms of an overdose until several days after receiving too much of LEVOTHYROXINE SODIUM FOR INJECTION.

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, fever, changes in period bleeding, convulsions and seizures (fits). Coma and death are also possible.

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

Missed Dose:

If you miss a dose, make sure it is administered as soon as possible. If it is almost time for your next dose, the missed dose should not be administered. Instead, the next regularly scheduled dose should be administered. Doses should not be doubled.

What are possible side effects from using LEVOTHYROXINE SODIUM FOR INJECTION?

These are not all the possible side effects you may have when taking LEVOTHYROXINE SODIUM FOR INJECTION. If you have any side effects not listed here, tell your healthcare professional.

Side effects may include:

- hair loss
- changes in menstrual cycle
- osteoporosis (bone loss)
- diarrhea
- vomiting
- headache
- excessive sweating
- tremors
- muscle weakness
- abdominal and leg cramps
- nervousness
- anxiety or irritability
- rapid changes in emotions
- fever

- flushing
- inability to tolerate heat
- fatigue
- trouble sleeping
- restlessness

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, increased blood pressure, shortness of breath			✓
Heart Failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			✓
Heart Attack: crushing chest pain that radiates to the left arm and/or jaw, sweating, nausea, vomiting, shortness of breath			✓
Angina (not enough oxygen to the heart muscle): discomfort in the shoulder, arm, back, throat, jaw or teeth; pain or pressure in the chest			✓
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			✓
Angioedema (swelling of tissue under the skin): difficulty breathing; swollen face, hands and feet, genitals tongue, throat; Swelling of the digestive tract causing diarrhea, nausea or vomiting		✓	
Elevations in liver enzymes		✓	
Pseudomotor cerebri (increased pressure in the brain in children): headaches, vison problems or complete vision loss, seeing double, ringing in the ears, pain in the arms			✓

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	
Hives or skin rash		✓	
Seizures (fits): muscle twitching, changes in emotions, confusion, loss of consciousness with uncontrollable shaking			✓

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

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

Keep in a safe place out of the reach and sight of children.

If you want more information about LEVOTHYROXINE SODIUM FOR INJECTION:

- 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 (www.avirpharma.com), or by calling 1-888-430-0436.

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