PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**EUTHYROX®**

Levothyroxine Sodium Tablets,

Tablets, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg

USP

Thyroid Hormone

ATC Code: H03AA01

EMD Serono, A Division of EMD Inc., Canada

2695 North Sheridan Way, Suite 200

Mississauga, Ontario L5K 2N6

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RECENT MAJOR LABEL CHANGES

1 Indications	10/2021
4 Dosage and Administration, 4.1 Dosing Considerations	10/2021
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	10/2021
7 Warnings and Precautions	08/2023

Sections and Subsections that are not applicable at the time of authorization are not listed.

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EUTHYROX (Levothyroxine Sodium tablets, USP) is indicated for:

Hypothyroidism

EUTHYROX is indicated as a replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism

Pituitary Thyrotropin (Thyroid-stimulating hormone, TSH) Suppression

EUTHYROX is indicated as an adjunct to surgery and radioiodine 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 EUTHYROX® in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. The use in pediatric population is associated with differences in safety or effectiveness and dosing precautions apply (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment and 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥65 years of age): EUTHYROX® is approved for use in the geriatric population. Clinical trials and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness and dosing precautions apply (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

EUTHYROX is contraindicated in:

- 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, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see 7 WARNINGS AND PRECAUTIONS, Autoimmune Polyglandular Syndrome).
- Patients with untreated pituitary insufficiency.
- 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.
- Pregnant women being treated with drugs for hyperthyroidism, such as methimazole and

propylthiouracil. Combination therapy of EUTHYROX and an antithyroid agent for hyperthyroidism is not indicated during pregnancy (see 7.1.1 Pregnant Women)

- Patients with acute myocardial infarction, acute myocarditis, or acute pancarditis. Treatment with EUTHYROX must not be initiated in these patients.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
Thyroid hormones, including EUTHYROX, 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 EUTHYROX ® is determined by the indication, and must individualized based on periodic assessment of the patient's clinical response and laboratory parameters (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, General).

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 EUTHYROX®, the frequency of dose titration, and the optimal full replacement dose must be individualized for every patient. The dose of EUTHYROX that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see 7 WARNINGS AND PRECAUTIONS, General).

Pediatrics
Congenital or acquired hypothyroidism:
In general, levothyroxine sodium therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development. Undertreatment and overtreatment should be avoided (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 7.1.3 Pediatrics).

For specific dosing instructions, see Tables 1a and 1b.

4.2 Recommended Dose and Dosage Adjustment

Hypothyroidism

Recommended dosage of EUTHYROX® are summarized in Table 1a and 1b, with additional details provided below.

Pediatric

The EUTHYROX recommended dose per body weight decreases with age (see Table 1a and 1b). However, in children with chronic or severe hypothyroidism or pre-existing cardiac insufficiency, EUTHYROX should be initiated gradually, with an initial dose of 25 mcg/day of EUTHYROX is recommended with increments of 25 mcg every 2-4 weeks until the desired effect is achieved.

Hyperactivity in an older child can be minimized if the starting dose is one-fourth of the recommended full replacement dose, and the dose is then increased on a weekly basis by an amount equal to one-fourth the full-recommended replacement dose until the full-recommended replacement dose is reached.

Newborns

The recommended starting dose of EUTHYROX in newborn infants is 10-15 mcg/kg/day. A lower starting dose (e.g., 25 mcg/day) should be considered in infants at risk for cardiac failure, and the dose should be increased in 4-6 weeks as needed based on clinical and laboratory response to treatment. In infants with very low (< 5 mcg/dL) or undetectable serum T4 concentrations, the recommended initial starting dose is 50 mcg/day of EUTHYROX.

Table 1a: DOSING AND ADMINISTRATION

MEDICAL CONDITION(S)	PATIENT POPULATION	STARTING DOSE	DOSING INCREMENT	INTERVAL FOR MONITORING/ DOSING INCREMENT	THERAPEUTIC GOAL
Congenital Hypothyroidism	Neonate	10 – 15 mcg/kg/day	12.5 mcg/day	2 wks (until normalization of TSH levels), 4-6 wks thereafter	Free-T_4 level in upper half of normal range
Congenital/ Acquired Hypothyroidism	Infants/Children	See table 1b	25 mcg/day	1-2 mos (until 1 y), 2-3 mos (until 3 y), 3-12 mos thereafter	Free-T_4 level in upper half of normal range, normal TSH
Congenital Hypothyroidism with risk of heart failure	Neonate	25 mcg/day	12.5 mcg/day	4-6 wks	Free-T_4 level in upper half of normal range, normal TSH
Severe Congenital Hypothyroidism (T_4 < 5mcg/dL)	Neonate	50 mcg/day	25 mcg/day	2-4 wks	Free-T_4 level in upper half of normal range, normal TSH
Hypothyroidism with Completed Growth and Puberty	Children	1.6 – 1.7 mcg/kg/day	25 – 50 mcg/day	6-8 wks	Normal TSH (age-specific reference range)
Hypothyroidism	Adults < 50 y	1.7 mcg/kg/day	25 – 50 mcg/day	6-8 wks	Normal TSH (0.5 and 2.0 mU/L)
	Adults > 50 y	25 – 50 mcg/day	12.5 – 25 mcg/day	6-8 wks	Normal TSH (0.5 and 2.0 mU/L)

Hypothyroidism with Cardiac Disease	Adults < 50 y	25 – 50 mcg/day	12.5 – 25 mcg/day	6-8 wks	Normal TSH (0.5 and 2.0 mU/L)
	Adults >50 y	12.5 – 25 mcg/day	12.5 – 25 mcg/day	4-6 wks	Normal TSH (0.5 and 3.0 mU/L)
Severe Hypothyroidism	Adults < 50 y	12.5 – 25 mcg/day	25 mcg/day	2-4 wks	Normal TSH (0.5 and 2.0 mU/L)
	Infants/Children	25 mcg/day	25 mcg/day	2-4 wks	Normal TSH (age-specific reference range)
Hypothyroidism (short period) or Recently Treated with Hyperthyroidism	Adults > 50 y	<1.7mcg/kg/ day	25 – 50 mcg/day	6-8 wks	Normal TSH (0.5 and 2.0 mU/L)
Hypothyroidism with Pregnancy	Pregnant Women	1.7 mcg/kg/day (Increased dose may be required)	25 – 50 mcg/day	4 wks (during 1st half of pregnancy), and at least once between week 26 and 32 6 wks postpartum	1st trimester: TSH <2.5 mU/L; 2nd trimester: TSH <3.0 mU/L; 3rd trimester: TSH <3.5 mU/L FT4 in the upper third of normal range
Secondary Hypothyroidism	Not Specified	**	**	**	Free-T_4 level in upper third of normal range
Tertiary Hypothyroidism	Not Specified	**	**	**	Free-T_4 level in upper third of normal range
Subclinical Hypothyroidism	Not Specified	25 – 50 mcg/day	Adjust as necessary	6-8 wks	Normal TSH (between 0.3 and 3.0 mU/L)
Well-differentiated (Papillary or Follicular) Thyroid Cancers)	Not Specified	> 2 mcg/kg/day	25 – 50 mcg/day	6 – 8 wks	TSH < 0.1 mU/L TSH <0.01 mU/L for patients with high risk tumors

**Depending on age, duration of hypothyroidism and cardiovascular risk factor

Table 1b: Levothyroxine Sodium Dosing Guidelines for Pediatric Hypothyroidism

AGE	**Daily Dose Per Kg 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, Pediatrics**).	

Subclinical Hypothyroidism

If this condition is treated, a lower EUTHYROX dose (e.g., 1 mcg/kg/day) than that used for full replacement may be adequate to normalize the serum TSH level. Patients who are not treated should be monitored yearly for changes in clinical status and thyroid laboratory parameters.

TSH Suppression in Well-differentiated Thyroid Cancer

The target level for TSH suppression in these conditions has not been established with controlled studies. In addition, the efficacy of TSH suppression for benign nodular disease is controversial. Therefore, the dose of EUTHYROX used for TSH suppression should be individualized based on the specific disease and the patient being treated.

In the treatment of well-differentiated (papillary and follicular) thyroid cancer, EUTHYROX is used as an adjunct to surgery and radioiodine therapy. Generally, TSH is suppressed to <0.1 mU/L, and this usually requires a EUTHYROX dose of greater than 2 µg/kg/day. However, in patients with high-risk tumors, the target level for TSH suppression may be <0.01 mU/L.

Treatment with thyroid hormones is given consistently during pregnancy and breast-feeding in particular. Dosage requirements may even increase during pregnancy (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, and 7.1.2 Breast Feeding).

HYPOTHYROIDISM IN ADULTS AND IN CHILDREN IN WHOM GROWTH AND PUBERTY ARE COMPLETE

(see 7 WARNINGS AND PRECAUTIONS). Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have been recently treated for hyperthyroidism or who have been hypothyroid for only a short time (such as a few months). The average full replacement dose of EUTHYROX is approximately 1.7 mcg/kg/day (e.g., 100-125 mcg/day for a 70 kg adult). Older patients may require less than 1 mcg/kg/day. Levothyroxine sodium doses greater than 200 mcg/day are seldom required. An inadequate response to daily doses < 300 mcg/day is rare and may indicate poor compliance, malabsorption, and/or drug interactions.

In elderly patients, in patients with coronary heart disease, and in patients with severe or long-existing hypothyroidism, special caution is required when initiating therapy with thyroid hormones: Treatment is initiated at a low dose, which is increased slowly and at lengthy intervals with frequent monitoring of thyroid hormones. A maintenance dose lower than that required for complete correction of TSH levels may be considered.

For most patients older than 50 years or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of 25-50 mcg/day of EUTHYROX is recommended, with gradual increments in dose at 6-8 week intervals, as needed. The recommended starting dose of EUTHYROX in elderly patients with cardiac disease is 12.5-25 mcg/day, with gradual dose increments at 4-6 week intervals. The EUTHYROX dose is generally adjusted in 12.5-25 µg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized.

In patients with severe hypothyroidism, the recommended initial EUTHYROX dose is 12.5-25 mcg/day with increases of 25 mcg/day every 2-4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized.

In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the levothyroxine

sodium dose should be titrated until the patient is clinically euthyroid and the serum free-T4 level is restored to the upper half of the normal range.

PEDIATRIC DOSAGE – CONGENITAL OR ACQUIRED HYPOTHYROIDISM (see 7 WARNINGS AND PRECAUTIONS)

4.4 Administration

Adults

EUTHYROX is administered as a single daily dose, preferably one-half to one hour before breakfast, with a full glass of water and swallowed whole. EUTHYROX should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (see Drug-Drug Interactions).

Pediatrics

Infants receive the entire dose at once at least 30 minutes before the first meal of the day.

EUTHYROX may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5-10 mL or 1-2 teaspoons) of water. This suspension can be administered by spoon or dropper. The suspension must be prepared freshly prior to each administration [DO NOT STORE THE SUSPENSION]. 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 EUTHYROX tablets (see Drug-Food Interactions).

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

Caution should be exercised when administering EUTHYROX 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 taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next regularly scheduled dose should be taken. Doses should not be doubled.

5 OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism (see 7 WARNINGS AND PRECAUTIONS, General and 8.1 Adverse Drug Reaction Overview). Overdose may cause symptoms of a significant increase in the metabolic rate. Signs and symptoms of thyrotoxicosis include exophthalmic goiter, weight loss, increased appetite, palpitations, nervousness, diarrhea, abdominal cramps, sweating, tachycardia, increased pulse and blood pressure, cardiac arrhythmias, angina pectoris, tremors, insomnia, heat intolerance, fever, and menstrual irregularities. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. In predisposed patients isolated cases of seizures have been reported when the individual dose tolerance limit was exceeded. Seizures have occurred in a child ingesting approximately 18 mg of EUTHYROX. Overdose of EUTHYROX may result in hyperthyroidism and could lead to symptoms of acute psychosis, especially in patients at risk of psychotic disorders. Symptoms may not necessarily be evident or may

not appear until several days after ingestion of EUTHYROX. Several cases of sudden cardiac death have also been reported in patients with many years of levothyroxine sodium abuse.

Treatment of Overdosage

This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. An elevated T3 level is a reliable indicator of overdose, more than elevated T4 or fT4 levels. EUTHYROX should be reduced in dose or temporarily discontinued and thyroid hormone should be monitored, if signs or symptoms of overdosage occur. If not contraindicated (e.g., by seizures, coma, or loss of the gag reflex), the stomach should be emptied by emesis or gastric lavage to decrease gastrointestinal absorption. Activated charcoal or cholestyramine may also be used to decrease absorption. Beta-sympathomimetic effects or central and peripheral increased sympathetic activity such as tachycardia, anxiety, agitation or hyperkinesia can be relieved by 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 T4 to T3. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Because T4 is highly 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

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300 mcg of levothyroxine sodium.	corn starch, croscarmellose sodium, gelatin, lactose monohydrate, and magnesium stearate *For a complete listing see Dosage Forms, Composition and Packaging section.*

The following are the color additives by tablet strength:

Strength (mcg)	Colour Additive(s)
25	FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake
50	None
75	FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake
88	FD&C Yellow No. 5 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake
100	D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake
112	D&C Red No. 27 Aluminum Lake
125	FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 5 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake
137	FD&C Blue No. 1 Aluminum Lake
150	FD&C Blue No. 2 Aluminum Lake
175	FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 3 Aluminum Lake
200	D&C Red No. 30 Aluminum Lake
300	D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake

6.1 Physical Characteristics

EUTHYROX (levothyroxine sodium tablets, USP) are round, biplanar (flat on both sides), beveled edged tablets with a score line on one side and "EM <strength>" on the other side. All strengths are supplied in bottles of 100 and 1000. They are color coded, and potency marked as follows:

Strength (mcg)	Color	Embossed Marking
25	orange	EM 25
50	white	EM 50
75	violet	EM 75
88	olive	EM 88
100	yellow	EM 100
112	pink	EM 112
125	brown	EM 125
137	blue	EM 137
150	blue	EM 150
175	purple	EM 175
200	pink	EM 200
300	green	EM 300

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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

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

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

Hypothyroidism and / or reduced control of hypothyroidism may occur when orlistat and EUTHYROX are co-administered (see Drug-Drug Interactions). It is recommended that patients taking orlistat with Euthyrox take both drugs at separate times. Thyroid hormone levels should be monitored more closely as the dose may need to be adjusted (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and 9 Drug Interactions).

Carcinogenesis and Mutagenesis

Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential, or effects on fertility of levothyroxine sodium. The synthetic T4 in EUTHYROX is identical to that produced naturally by the human thyroid gland. Although there has been a reported association between prolonged thyroid hormone therapy and breast cancer, this has not been confirmed. Patients receiving EUTHYROX for appropriate clinical indications should be titrated to the lowest effective replacement dose.

Cardiovascular

EUTHYROX is contraindicated in patients with acute myocardial infarction, acute myocarditis, or acute pancarditis (see 2 CONTRAINDICATIONS). Exercise caution when administering EUTHYROX to patients with other cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, EUTHYROX 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, Administration). If cardiac symptoms develop or worsen, the EUTHYROX dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Even slight drug-induced hyperthyroidism must be avoided in patients with coronary insufficiency, heart failure or tachycardiac arrhythmias. Overtreatment with EUTHYROX may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving EUTHYROX therapy should be

monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with EUTHYROX. Concomitant administration of EUTHYROX 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.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. It is not expected that EUTHYROX has any influence on the ability to drive and use machines, if used as recommended. 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.

Patients treated concomitantly with EUTHYROX® and orlistat should be monitored for changes in thyroid function (see 9 DRUG INTERACTIONS). Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism may involve a decreased absorption of iodine salts and/or levothyroxine.

Hypothalamic/Pituitary Hormone Deficiencies

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

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

Bone Mineral Density

Long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density. 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. In postmenopausal women with hypothyroidism and an increased risk of osteoporosis supra-physiological serum levels of levothyroxine sodium have to be avoided and close monitoring of the thyroid function is recommended. Therefore, it is recommended that patients should be given the minimum dose of EUTHYROX necessary to achieve the desired clinical and biochemical response.

Myxedema Coma

Myxedema coma represents the extreme expression of severe hypothyroidism and is considered a medical emergency. It 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 EUTHYROX®, 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 EUTHYROX® 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. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with EUTHYROX. 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 sodium (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).

Monitoring and Laboratory Tests

General

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

The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. The choice of laboratory tests depends on various factors including the etiology of the underlying thyroid disease, the presence of concomitant medical conditions, including pregnancy, and the use of concomitant medications (see 9 DRUG INTERACTIONS, 9.4 Drug-drug Interactions and 9.7 Drug-Laboratory Test Interactions). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of levothyroxine sodium may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T4 potency of the drug product.

Where thyroid autonomy is suspected, a TRH test or a suppression scintigram is recommended before initiation of treatment.

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 (9.7 Drug-Laboratory Test interactions). 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 has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed.

Adults

In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels (using a sensitive assay) alone may be used to monitor therapy. The frequency of TSH monitoring during levothyroxine sodium dose titration depends on the clinical situation but it is generally recommended at 6-8 week intervals until normalization. When the optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6-12 months, depending on the clinical situation, and whenever there is a change in the patient's status. It is recommended that a physical examination and a serum TSH measurement be performed at least annually in patients receiving EUTHYROX (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Subclinical Hypothyroidism).

Pediatrics

In patients with congenital hypothyroidism, the adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free-T4. During the first three years of life, the serum total- or free-T4 should be maintained at all times in the upper half of the normal range. While the aim of therapy is to also normalize the serum TSH level, this is not always possible in a small percentage of patients, particularly in the first few months of therapy. TSH may not normalize due to a resetting of the pituitary-thyroid feedback threshold as a result of in utero hypothyroidism. Failure of the serum T4 to increase into the upper half of the normal range within 2 weeks of initiation of levothyroxine sodium therapy and/or of the serum TSH to decrease below 20 mU/L within 4 weeks should alert the physician to the possibility that the child is not receiving adequate therapy. Careful inquiry should then be made regarding compliance, dose of medication administered, and method of administration prior to raising the dose of EUTHYROX.

The recommended frequency of monitoring of TSH and total- or free-T4 in children is as follows: at 2 and 4 weeks after the initiation of treatment; every 1-2 months during the first year of life; every 2-3 months between 1 and 3 years of age; and every 3 to 12 months thereafter until growth is completed. More frequent intervals of monitoring may be necessary if poor compliance is suspected, or abnormal values are obtained. It is recommended that TSH and T4 levels, and a physical examination, if indicated, be performed 2 weeks after any change in EUTHYROX dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 7.1.3 Pediatrics; and 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations).

Secondary (Pituitary) and Tertiary (Hypothalamic) Hypothyroidism

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

Once levothyroxine sodium treatment has been established, in case of switching the brand it is recommended to adjust the dosage following the patient's clinical response and laboratory test.

Psychiatric

When initiating EUTHYROX therapy in patients at risk of psychotic disorders, it is recommended to start at a low EUTHYROX 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.

Sensitivity/Resistance

EUTHYROX contains lactose; therefore, its use is not recommended in patients with rare hereditary problems of galactose-intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Reproductive Health: Female and Male Potential

Fertility

EUTHYROX should not be used 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 women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Furthermore, there is no evidence of drug-induced teratogenicity and/or foeto-toxicity in humans at the recommended therapeutic dose level. (see 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations) Therefore, the possibility of fetal harm appears remote. EUTHYROX should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth, and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. During pregnancy, serum T4 levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women who are maintained on EUTHYROX 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. Trimester specific TSH reference values are recommended (see 4 DOSAGE AND ADMINISTRATION). An elevated serum TSH level should be corrected by an increase in the dose of EUTHYROX. Since postpartum TSH levels are similar to preconception values, the EUTHYROX dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-weeks postpartum.

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

7.1.2 Breast Feeding

Minimal amounts of thyroid hormones are excreted in human milk. While caution should be exercised when EUTHYROX is administered to a breast-feeding woman, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.

7.1.3 Pediatrics

Hemodynamic 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.

In children in whom a diagnosis of permanent hypothyroidism has not been established, it is recommended that EUTHYROX administration be discontinued for a 30-day trial period, but only after

the child is at least 3 years of age. Serum T4 and TSH levels should then be obtained. If the T4 is low and the TSH high, the diagnosis of permanent hypothyroidism is established, then EUTHYROX therapy should be reinstituted. If the T4 and TSH levels are normal, euthyroidism may be assumed and, therefore, the hypothyroidism can be considered to have been transient. In this instance, however, the physician should carefully monitor the child and repeat the thyroid function tests if any signs or symptoms of hypothyroidism develop. In this setting, the clinician should have a high index of suspicion of relapse. If the results of the levothyroxine sodium withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.

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 EUTHYROX by half during the 30-day trial period. If, after 30 days, the serum TSH is elevated above 20 mU/L, the diagnosis of permanent hypothyroidism is confirmed, and full replacement therapy should be resumed. However, if the serum TSH has not risen to greater than 20 mU/L, levothyroxine sodium treatment should be discontinued for another 30-day trial period followed by repeat serum T4 and TSH testing.

The presence of concomitant medical conditions should be considered in certain clinical circumstances and, if present, appropriately treated (see 7 WARNINGS AND PRECAUTIONS, General).

Congenital hypothyroidism

(see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Pediatrics; and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment)

Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, with cardiovascular anomalies (pulmonary stenosis, atrial septal defect, and ventricular septal defect) being the most common association.

Rapid restoration of normal serum T4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, EUTHYROX therapy should be initiated immediately upon diagnosis and is generally continued for life.

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

The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment has been associated with craniosynostosis in infants and may adversely affect the tempo of brain maturation and accelerate the bone age, with resultant premature closure of the epiphyses and compromised adult stature.

ACQUIRED HYPOTHYROIDISM IN PEDIATRIC PATIENTS

The patient should be monitored closely to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

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 7 WARNINGS AND PRECAUTIONS, Cardiovascular; and 4 DOSAGE AND ADMINISTRATION, Administration).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Clinical signs of hyperthyroidism may occur in case of overdose, if the individual tolerance limit for levothyroxine sodium is exceeded, or if the dose is increased too fast at the start of treatment. In such cases the daily dose has to be reduced or the medication withdrawn for several days. Therapy may carefully be resumed once the adverse reactions have disappeared (see 7 WARNINGS AND PRECAUTIONS, General; and 5 OVERDOSAGE).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following symptoms are typical:

Cardiac disorders	palpitations, tachycardia, cardiac arrythmias (e.g atrial fibrillation and extrasystoles), increased pulse and blood pressure, heart failure, angina pectoris, myocardial infarction, cardiac arrest;
Gastrointestinal	diarrhea, vomiting, abdominal cramps
General	fatigue, heat intolerance, fever, excessive sweating;
Immune System Disorders	Hypersensitivity reactions to inactive ingredients have occurred. 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 sodium itself is not known to occur.
Investigational	decreased bone mineral density; elevations in liver function tests
Metabolism and nutrition disorders	increased appetite, weight loss
Musculoskeletal and connective tissue	tremors, muscle weakness, cramps, slipped capital femoral epiphysis in children. Excessive dose may result in craniosynostosis and premature closure of the epiphyses in children (with resultant compromised adult height)
Nervous system	headache, seizures, pseudotumour cerebri

Psychiatric disorders	hyperactivity, nervousness, restlessness, anxiety, irritability, emotional lability and insomnia
Reproductive System	Menstrual Irregularities, impaired fertility
Respiratory System	Dyspnea
Skin and subcutaneous tissue disorders	alopecia (generally transient)
Vascular disorders	Flushing

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to EUTHYROX. 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 2.

9.3 Drug-Behavioural Interactions

This information is not available for this drug product.

9.4 Drug-Drug 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 2: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that may reduce TSH secretion – the reduction is not sustained; therefore, hypothyroidism does not occur			
Dopamine/Dopamine Agonists Glucocorticoids Octreotide	CT	Use of these agents may result in a transient reduction in TSH secretion.	Reduction when administered at the following doses: Dopamine (1 mcg/kg/min); Glucocorticoids (hydrocortisone 100 mg/day or equivalent); Octreotide (> 100 mcg/day).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that alter thyroid hormone secretion			
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism			
Aminoglutethimide Amiodarone Iodide (including iodine-containing radiographic contrast agents) Lithium Methimazole Propylthiouracil (PTU) Sulfonamides Tolbutamide	CT	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients.	The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism			
Amiodarone Iodide (including iodine-containing radiographic contrast agents) Sertraline Chloroquinone Proguanil	CT	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). Sertraline, Chloroquinone / Proguanil decrease the efficacy of levothyroxine sodium and increase the serum TSH level	Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that may decrease T_4 absorption, which may result in hypothyroidism			
Sucralfate Antacids -Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Ion Exchange Resins - Kayexlate Iron containing medicinal ingredients Ferrous Sulfate Orlistat Sevelamer	CT	Concurrent use may reduce the efficacy of levothyroxine sodium by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Ion exchange resins inhibit the absorption of levothyroxine sodium. The mechanism may involve a decreased absorption of iodine salts and/or levothyroxine sodium. Sevelamer also decreases levothyroxine sodium absorption.	Calcium carbonate may form an insoluble chelate with levothyroxine sodium, and ferrous sulfate likely forms a ferric-thyroxine complex. It is recommended that EUTHYROX be administered at least 2 hours prior to the administration of aluminium-containing and iron-containing medicinal products. The same applies to calcium carbonate. Ion exchange resins must be administered 4-5 hours prior to EUTHYROX therapy. Patients treated concomitantly with Orlistat and EUTHYROX should be monitored for changes in thyroid function. Patients on EUTHYROX and concomitant use of Sevelamer should be monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the EUTHYROX dose has to be adjusted.
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	CT	Increase serum Thyroxine Binding Globulin (TBG) concentration	N/A
Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	CT	Decrease serum TBG concentration	N/A

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that may cause protein-binding site displacement			
Furosemide (> 80 mg IV) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs -Fenamates -Phenylbutazone Salicylates (> 2 g/day) Dicumarol Furosemide in high doses (250mg) Clofibrate	CT	Administration of these agents with levothyroxine sodium can displace levothyroxine sodium from plasma proteins, resulting in an elevated FT_4 fraction. 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%.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that may alter T_4 and T_3 metabolism			
Drugs that may increase hepatic metabolism, which may result in hypothyroidism			
Carbamazepine Hydantoins (e.g. Phenytoin) Barbiturates (e.g. Phenobarbital) Rifampin	CT	Stimulation of hepatic microsomal drug-metabolizing enzyme activity by drugs like phenytoin may cause increased hepatic metabolism / degradation/ clearance of levothyroxine sodium, resulting in increased levothyroxine sodium requirements. On the other hand, phenytoin may influence the effect of levothyroxine sodium by displacing levothyroxine sodium from plasma proteins resulting in an elevated fT4 and fT3 fraction . Carbamazepine reduces serum protein binding of levothyroxine sodium and total- and free-T_4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.	Close monitoring of thyroid hormone parameters is recommended.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that may decrease T_4 5'-deiodinase activity			
Iodine containing contrast media Amiodarone Beta-adrenergic antagonists / beta sympatholytics (e.g., Propranolol > 160 mg/day) Glucocorticoids (e.g., Dexamethasone 4 mg/day) Propylthiouracil (PTU)	CT	Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (>160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. Due to its high iodine content amiodarone can trigger hyperthyroidism as well as hypothyroidism.	It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (see above). In EUTHYROX patients with concomitant use of Amiodarone, particular caution is advised in the case of nodular goitre with possibly unrecognised autonomy.
Miscellaneous			
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	CT	Levothyroxine sodium may intensify the effect of anticoagulants by displacing them from plasma protein bounds which may increase the risk of haemorrhage, e.g. CNS or gastrointestinal bleeding, especially in elderly patients . Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis.	Check the coagulation parameters regularly at the start of and during concomitant therapy. Prothrombin time can be carefully monitored in patients taking EUTHYROX and if necessary, the anticoagulant dose has to be altered.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Antidepressants - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline, chloroquine/proguanil)	CT	Concurrent use of tri/tetracyclic antidepressants and levothyroxine 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. Sertraline, chloroquine/proguanil: these substances decrease the efficacy of levothyroxine sodium and increase the serum TSH level
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidediones - Insulin	CT	Levothyroxine sodium may reduce the effect of anti-diabetics. If necessary, the anti-diabetic dose has to be adjusted.	It is necessary to check blood glucose levels frequently at the start of thyroid hormone therapy or when thyroid hormone therapy is changed or discontinued.
Cytokines	CT	Therapy with interferon-α has been associated with the development of antithyroid microsomal antibodies in 20% of patients, and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients.	Interferon-β and -γ have not been reported to cause thyroid dysfunction.
Digitalis Glycosides	CT	Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides.	The therapeutic effects of digitalis glycosides may be reduced by levothyroxine sodium.
Growth Hormones - Somatrem - Somatropin	CT	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure.	Untreated hypothyroidism may interfere with growth response to growth hormone.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Ketamine	CT	Concurrent use may produce marked hypertension and tachycardia.	Cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators (e.g., Theophylline)	CT	Decreased theophylline clearance may occur in hypothyroid patients.	Clearance returns to normal when the euthyroid state is achieved.
Oestrogens	CT	Women using oestrogen-containing contraceptives or postmenopausal women under hormone-replacement therapy may have an increased need for levothyroxine sodium.	N/A
Protease inhibitors	CT	Protease inhibitors (e.g. ritonavir, indinavir, lopinavir) may influence the effect of levothyroxine sodium.	Close monitoring of thyroid hormone parameters is recommended. If necessary, the levothyroxine sodium dose has to be adjusted.
Proton Pump Inhibitors	T	Plasma concentration of levothyroxine (thyroxine) is possibly reduced by Proton Pump Inhibitors	Monitoring of TSH plasma level is recommended
Radiographic Agents	CT	Thyroid hormones may reduce the uptake of ^{123}I, ^{131}I, and ^{99m}Tc.	N/A
Sympathomimetics	CT	Concurrent use may increase the effects of sympathomimetics or thyroid hormone.	Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Tyrosine-kinase inhibitors	CT	Tyrosine-kinase inhibitors (e.g. imatinib, sunitinib) may decrease the efficacy of levothyroxine sodium.	Therefore, it is recommended that patients are monitored for changes in thyroid function at the start or end of concomitant treatment. If necessary, the levothyroxine sodium dose has to be adjusted.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Chloral Hydrate Ciprofloxacin Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	C, CT	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.	N/A

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

9.5 Drug-Food Interactions

Consumption of certain foods may affect levothyroxine sodium absorption thereby necessitating adjustments in dosing. Cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the GI tract. Soy containing compounds including soybean flour (infant formula) can also decrease the intestinal absorption of levothyroxine sodium. A dosage adjustment of EUTHYROX particularly at the beginning or after termination of nutrition with soy supplements may be necessary.

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

Changes in TBG concentration must be considered when interpreting T4 and T3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free-T4 index (FT4I). Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy (see also Table 2). Familial hyper- or hypo-thyroxine binding globulinemia have been described, with the incidence of TBG deficiency approximating 1 in 9000.

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

Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin-stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyroxine (T4) and L-triiodothyronine (T3), by the thyroid gland. Circulating serum T3 and T4 levels exert a feedback effect on both TRH and TSH secretion. When serum T3 and T4 levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increase.

The mechanisms by which thyroid hormones exert their physiologic actions are not completely understood, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T3 and T4 diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins.

Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development.

The physiological actions of thyroid hormones are produced predominantly by T3, the majority of which (approximately 80%) is derived from T4 by deiodination in peripheral tissues.

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

Levothyroxine sodium is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of Hashimoto's thyroiditis, and as adjunctive therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (see 1 INDICATIONS AND CLINICAL USE; 7 WARNINGS AND PRECAUTIONS; and 4.2 Recommended Dose and Dosage Adjustment, TSH Suppression in Well-differentiated Thyroid Cancer).

10.2 Pharmacodynamics

EUTHYROX (Levothyroxine sodium tablets, USP) contains synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T4) sodium]. Synthetic T4 is identical to that produced in the human thyroid gland. Levothyroxine (T4) sodium has an empirical formula of C15H10I4NnaO4 • H2O, molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown in 13 PHARMACEUTICAL INFORMATION:

10.3 Pharmacokinetics

Table 3: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	t½ (days)	Protein Binding (%)[2]
Levothyroxine sodium (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				

Absorption

Orally given levothyroxine sodium is absorbed almost exclusively in the upper small intestine (jejunum and upper ileum). Depending on the galenic formulation absorption can range from 40% and can amount up to 80%. tmax is approximately 5 - 6 hours.

The relative bioavailability of levothyroxine sodium tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%. T4 absorption is increased by fasting and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T4. Absorption may also decrease with age. In addition, many drugs and foods affect T4 absorption (see 9 DRUG INTERACTIONS, Drug-Food Interactions).

Distribution:

Levothyroxine sodium exhibits an extremely high binding to specific transport proteins of about 99.97%. This protein hormone binding is not covalent and so the bound hormone in plasma is in continuous and very rapid exchange with the fraction of the free hormone. The volume of distribution amounts to about 10 12 L. The liver contains ⅓ of the entire extra-thyroidal levothyroxine sodium, which is rapidly exchangeable with the levothyroxine sodium in serum.

Circulating thyroid hormones are greater than 99% bound to plasma proteins, include thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (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, Special Populations, 7.1.1 Pregnant Women).

Metabolism:

Thyroid hormones are metabolised mainly in the liver, kidneys, brain and muscles. T_4 is slowly eliminated (see Table 3). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3, with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (rT_3). T_3 and rT_3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination

The half-life of levothyroxine sodium is on average 7 days. In hyperthyroidism it is shorter (3 –4 days) and in hypothyroidism it is longer (approx. 9 - 10 days). The metabolites are excreted with urine and faeces. The overall metabolic clearance for levothyroxine sodium is about 1.2 L plasma per day.

A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T4 is eliminated in the stool. Urinary excretion of T4 decreases with age. Due to its high protein binding levothyroxine sodium cannot be eliminated via haemodialysis or haemoperfusion.

11 STORAGE, STABILITY AND DISPOSAL

Store between 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from light. Protect from moisture. Keep in a safe place out of the reach of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

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

Proper name: Sodium Levothyroxine (L-T4, Na)

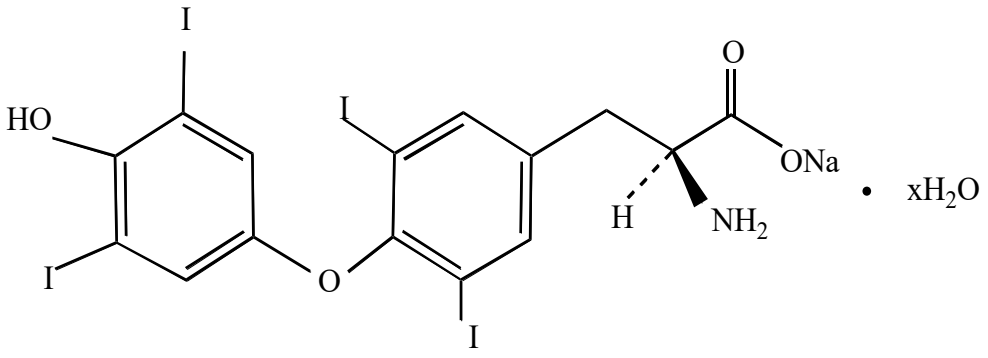
Chemical name: USP: (1) L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt (2) Monosodium L-thyroxine hydrate

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

Molecular formula and molecular mass: $C_{15}H_{10}I_4NnaO_4 \bullet xH_2O$

798.85g/mol (anhydrous)

Structural formula:



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

Solubility: Very slightly soluble in water

Slightly soluble in ethanol

Soluble in alkali hydroxide solutions

Solvent	g/100 mL
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

14.2 Study Results

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

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

A further study was conducted in seventeen postmenopausal women with subclinical hypothyroidism and no prior history of thyroid disease. Patients were randomly assigned to levothyroxine sodium treatment or no treatment and followed prospectively. Patients in the treatment group had similar initial serum TSH concentrations but were slightly older (68 ± 7 years versus 60 ± 5 years [p <0.02]).

The average dose of levothyroxine sodium needed to normalize serum TSH concentration was 0.072 ± 0.027 mg. Bone mineral determinations were not significantly different between the two groups at baseline.

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

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

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

Levothyroxine sodium therapy, at an average dose of 10 to 14 mcg/kg/day, was begun immediately after diagnosis, and serum concentrations of total thyroxine, triiodothyronine, reverse triiodothyronine and TSH were determined serially. Serum concentration of total and free thyroxine became normal within 1 week of the start of therapy in all groups. Despite a similarly mild degree of hypothyroidism at diagnosis in infants with dyshormonogenesis or with ectopia or hypoplasia, those with dyshormonogenesis had a more sensitive response to initial thyroid hormone replacement therapy than did patients with thyroid dysgenesis, as judged by levothyroxine sodium dose and TSH suppression. It was concluded that prompt restoration of clinical and biochemical euthyroidism during early infancy with doses of levothyroxine sodium between 10 to 14 mcg/kg/day was a safe and effective method of therapy for children with congenital hypothyroidism.

14.3 Comparative Bioavailability Studies

The bioavailability of levothyroxine may differ to some extent among marketed brands. Once the patient is stabilized on a particular brand of levothyroxine sodium, caution should be exercised when a change in drug product brand is implemented. If a switch to another levothyroxine-containing product is required, there is a need to undertake close clinical and biological monitoring during the transition period due to a potential risk of imbalance. In some patients, a dose adjustment could be necessary.

One study demonstrated that the pharmacokinetics of exogenous levothyroxine sodium following administration of the test tablet formulation are similar to those of an oral solution of the drug. The pharmacokinetic profiles of both treatments were almost superimposable, particularly in the post-absorption phase. Analysis of Variance (ANOVA) performed on the log-transformed AUC0-t and Cmax of T4 did not detect any significant difference between the test formulation and the reference oral solution. The T4 geometric mean test: reference ratios for AUC0-t and Cmax were 98% (95% geometric C.I., 92 – 106%) and 98% (95% geometric C.I., 90 – 106%), respectively (see Table 4). As evidenced by the geometric T4 AUC0-t and Cmax mean ratios and the corresponding 95% confidence intervals, bioavailability of T4 from the test formulation was equivalent to that of an oral solution of T4. It has been reported that approximately 80% of endogenous T3 is obtained by metabolism of T4 in the liver and kidneys. The suppression of T3 serum concentrations observed for both treatments, after correcting for baseline, was therefore unexpected. It may be reasonable to surmise that the liver may be an unimportant organ for the metabolism of T4 to T3. Perhaps, this metabolic pathway exists mainly in the kidneys or within the thyroid gland itself. EMD Serono's Levothyroxine Sodium Tablets, 2 x 300 mcg, were found to have a pharmacokinetic profile and T4 bioavailability similar to an equivalent dose of an oral solution of the drug. Exogenously administered T4 may suppress T3 serum levels in healthy individuals.

Table 4: Summary of T_4 Pharmacokinetic Parameters

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 µg) vs. Oral Solution 600 mcg** Corrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (mcg.h/dL)	146.94 149.29(19.18)	148.41 151.99(20.15)	98.4	91.6-105.7
AUC_I# (mcg.h/dL)				
C_{max} (mcg/dL)	6.49 6.60(19.85)	6.62 6.77(22.30)	97.9	90.3-106.1
T_{max}§ (h)	2.46(38.62)	1.73(45.09)		

* Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

† Levothyroxine Sodium, Oral solution, 600 µg (purchased in the United States and manufactured by American Pharmaceutical Partners Inc.)

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 µg) vs. Oral Solution 600 mcg** Uncorrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (mcg.h/dL)	502.70 506.81(13.18)	507.76 511.61(14.27)	98.8	96.5-102.0
AUC_I# (mcg.h/dL)				
C_{max} (mcg/dL)	13.46 13.57(13.19)	13.60 13.80(15.43)	98.6	94.7-102.6
T_{max}§ (h)	4.35(49.43)	3.02(47.68)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

† Levothyroxine Sodium, Oral solution, 600 µg (purchased in the United States and manufactured by American Pharmaceutical Partners Inc.)

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

Dosage-form equivalence between the 50 mcg and 100 mcg strengths of EMD Serono's Levothyroxine Sodium Tablets was evaluated in a study involving 24 healthy volunteers.

Analysis of Variance (ANOVA) performed on the log-transformed AUC0-t, Cmax, and Tmax of T4 did not detect any significant difference between the 50 mcg and 100 mcg strengths. The T4 geometric mean test: reference ratios (95% geometric C.I.) For AUC0-t and Cmax were 97% (89 – 106%) and 94% (86 – 103%), respectively (see Table 5).

Table 5: Summary of T_4 Pharmacokinetic Parameters

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (12 x 50 mcg vs. 6 x 100 mcg dose)** Corrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (mcg.h/dL)	146.94 152.02(25.95)	151.41 156.64(25.39)	97.0	88.5-106.4
AUC_I# (mcg.h/dL)				
C_{max} (mcg/dL)	6.05 6.24(24.36)	6.49 6.74(29.97)	93.8	85.7-102.7
T_{max}§ (h)	2.67(35.58)	2.40(47.50)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 12 x 50 µg tablets
† Levothyroxine Sodium, EMD Serono Canada Inc., 6 x 100 µg tablets
# AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)
§ Expressed as arithmetic mean (CV%)

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (12 x 50 mcg vs. 6 x 100 mcg dose)** Uncorrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (mcg.h/dL)	497.70 501.41(12.44)	507.76 511.77(16.49)	98.7	95.4-101.6
AUC_I# (mcg.h/dL)				
C_{max} (mcg/dL)	13.06 13.17(14.58)	13.46 13.74(18.41)	96.4	92.1-100.9
T_{max}§ (h)	4.73(46.93)	4.15(54.46)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 12 x 50 µg tablets
† Levothyroxine Sodium, EMD Serono Canada Inc., 6 x 100 µg tablets
# AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)
§ Expressed as arithmetic mean (CV%)

As evidenced by the geometric AUC0-t and Cmax mean ratios and the corresponding 95% confidence intervals, bioavailability of T4 from equal doses of the 50 mcg and 100 mcg strengths are equivalent. EMD Serono's 50 mcg and 100 mcg strengths of Levothyroxine Sodium Tablets exhibit dosage form equivalence or dosage-strength proportionality.

Dosage-form equivalence between the 300 mcg and 100 mcg strengths of EMD Serono's Levothyroxine Sodium Tablets was evaluated in a study involving 24 healthy volunteers.

Analysis of Variance (ANOVA) performed on the log-transformed AUC0-t, Cmax, and Tmax of T4 did not detect any significant difference between the 300 mcg and 100 mcg strengths. The T4 geometric mean test:reference ratios (95% geometric C.I.) For AUC0-t and Cmax were 114% (104 – 124%) and 104% (96 – 113%), respectively (see Table 6).

Table 6: Summary of T_4 Pharmacokinetic Parameters

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 mcg vs. 6 x 100 mcg dose)** Corrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (mcg.h/dL)	165.67 168.33(15.33)	146.94 150.35(22.86)	113.6	104.0-124.1
AUC_I# (mcg.h/dL)				
C_{max} (mcg/dL)	5.99 6.13(21.21)	5.75 5.90(21.69)	104.0	95.7-113.0
T_{max}§ (h)	2.83(83.75)	2.63(50.95)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 6 x 100 µg tablets

† Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 mcg vs. 6 x 100 mcg dose)** Uncorrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (mcg.h/dL)	518.01 520.83(10.03)	507.76 507.92(8.96)	102.1	99.5-105.4
AUC_I# (mcg.h/dL)				
C_{max} (mcg/dL)	12.94 13.12(13.64)	12.94 13.03(10.44)	100.3	96.6-104.1
T_{max}§ (h)	4.96(95.36)	4.58(55.02)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 6 x 100 µg tablets

† Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

As evidenced by the geometric AUC0-t and Cmax mean ratios and the corresponding 95% confidence intervals, bioavailability of T4 from equal doses of the 300 mcg and 100 mcg strengths are equivalent. EMD Serono's 300 mcg and 100 mcg strengths of Levothyroxine Sodium Tablets exhibit dosage form equivalence and dosage-strength proportionality.

A randomized, 2-way crossover, bioavailability study comparing levothyroxine sodium 0.3 mg tablets and Synthroid® 0.3 mg tablets (by Abbott Laboratories USA) administered as 2 x 0.3 mg tablets was conducted. This study was conducted in healthy subjects and under fasting conditions.

Table 7: Summary Table of the Comparative Bioavailability Data for Single-Dose Study Comparing Levothyroxine sodium 0.3 mg Tablet and Synthroid® 0.3 mg Tablet (2 x 0.3 mg levothyroxine sodium tablet)

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 mcg vs. 2 x 300 mcg dose)** Corrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (ng.h/mL)	1759.50 1800.80 (22.22)	1639.98 1689 (23.11)	107.29%	98.66%-116.67%
AUC_I# (ng.h/mL)				
C_{max} (ng/mL)	73.32 74.40 (17.35)	68.06 69.20 (17.43)	107.73%	100.77%-115.16%
T_{max}§ (h)	2.88 (25.25)	2.83 (49.82)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

† Levothyroxine Sodium, Synthroid ® by Abbott Laboratories USA (purchased in USA)., 2 x 300 mcg tablets

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 mcg vs. 2 x 300 mcg dose)** Uncorrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (ng.h/mL)	5240.94 5275.11(11.82)	5153.56 5180.68(10.56)	101.70%	98.46%-105.04%
AUC_I# (ng.h/mL)				
C_{max} (ng/mL)	145.83 146.76 (11.97)	141.28 141.90 (9.77)	103.22%	99.44%-107.15%
T_{max}§ (h)	2.88 (25.25)	2.83 (49.82)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

† Levothyroxine Sodium, Synthroid ® by Abbott Laboratories USA (purchased in USA)., 2 x 300 mcg tablets

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

A randomized, 2-way crossover, bioavailability study comparing levothyroxine sodium 0.3 mg tablets and Levoxyl® 0.3 mg tablets (by Jones Pharma Inc., USA) administered as 2 x 0.3 mg tablets was conducted. This study was conducted in healthy subjects and under fasting conditions.

Table 8: Summary Table of the Comparative Bioavailability Data for Single-Dose Study Comparing Levothyroxine sodium 0.3 mg Tablet and Levoxyl® 0.3 mg Tablet (2 x 0.3 mg levothyroxine sodium tablet)

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 mcg vs. 2 x 300 mcg dose)** Corrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (ng.h/mL)	1643.25 1745.94 (31.58)	1778.18 1795.73 (21.85)	94.42%	82.60%-107.92%
AUC_I#(ng.h/mL)				
C_{max} (ng/mL)	69.21 71.67 (24.65)	70.63 71.05 (21.64)	100.12%	93.51%-107.19%
T_{max}§ (h)	2.38 (38.14)	2.59 (32.96)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

† Levothyroxine Sodium, Levoxyl ® (Jones Pharma Inc., USA, purchased in the USA)., 2 x 300 µg tablets

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA **Levothyroxine sodium 600 mcg (2 x 300 mcg vs. 2 x 300 mcg dose)** Uncorrected for Baseline From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	95% Confidence Interval
$AUC_{T(0-48)}$ (ng.h/mL)	4915.58 5054.55 (19.34)	5070.23 5151.98 (16.13)	96.95%	90.52%-103.84%
AUC_I#(ng.h/mL)				
C_{max} (ng/mL)	139.61 141.90 (16.28)	139.04 140.98 (15.46)	100.41%	97.20%-103.73%
T_{max}§ (h)	2.38 (38.14)	2.59 (32.96)		

*Levothyroxine Sodium, EMD Serono Canada Inc., 2 x 300 µg tablets

† Levothyroxine Sodium, Levoxyl ® (Jones Pharma Inc., USA, purchased in the USA)., 2 x 300 mcg tablets

AUC_I cannot reliably be calculated due to the nature of the study design and pharmacokinetics of Levothyroxine sodium (T½ = 7 days)

§ Expressed as arithmetic mean (CV%)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Excess thyroid hormone decreases bone mineral density (BMD), a potential problem in managing patients with differentiated thyroid carcinoma and nontoxic goiter who require lifelong TSH-suppressive doses of thyroid hormone. The effect of thyroid hormone excess on vertebral and femoral BMD and the role of hypogonadism in modulating this effect was studied in a rat model. The potential role of calcitonin in preventing thyroid hormone-associated bone loss was also investigated. A total of 40 male Sprague-Dawley rats were divided into four groups. Groups 1 and 2 were orchidectomized; groups 3 and 4 were sham operated. Groups 1 and 3 received 20 mcg intraperitoneal L-thyroxine per 100 g body weight daily for 3 weeks; groups 2 and 4 received vehicle IP. Another 40 rats were divided into four groups with groups 1 and 2 receiving L-thyroxine and 3 and 4 receiving calcitonin, 2.5U per 100 g body weight, subcutaneously for 3 weeks. Bone mineral density of the L4 and 5 and the right femur were measured by dual-energy x-ray absorptiometry at baseline and at the end of the study. Orchidectomy decreased femoral ($p < 0.05$) but not lumbar BMD. The administration of excess L-Thyroxine decreased femoral (cortical) BMD in both sham operated ($p < 0.05$) and orchidectomized rats ($p < 0.05$) without affecting lumbar (trabecular) BMD. Calcitonin increased lumbar BMD in both vehicle ($p < 0.001$) and L-thyroxine treated rats ($p < 0.001$). However, calcitonin did not affect femoral BMD in vehicle-treated rats and did not prevent the L-thyroxine induced femoral bone loss. Serum tartrate-resistant acid phosphatase (TRAP) was increased in the L-thyroxine treated ($p < 0.001$) and the orchidectomized ($p < 0.05$) rats. Calcitonin had no effect on TRAP activity and did not prevent the L-Thyroxine induced increase in TRAP. Neither excess L-thyroxine nor orchidectomy affect osteocalcin concentrations. Calcitonin decreased serum osteocalcin concentrations, alone ($p < 0.05$) and in the presence of excess L-thyroxine ($p < 0.05$). It was concluded that large doses of L-thyroxine administered to the rat preferentially decreased femoral BMD. Short-term hypogonadism decreases femoral but not lumbar BMD and does not make the lumbar spine more susceptible to the potential thyroid hormone-induced bone loss. Calcitonin increases lumbar BMD but does not prevent the thyroid hormone-induced decrease in femoral BMD.

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrEUTHYROX®

Levothyroxine Sodium Tablets, USP

Read this carefully before you start taking **EUTHYROX** 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 **EUTHYROX**.

Serious Warnings and Precautions
Thyroid hormones, including EUTHYROX, either alone or with other medicines, should not be used to treat obesity or for weight loss. Larger doses may cause serious or life-threatening side effects especially when taken together with medications used for weight loss.

What is EUTHYROX used for?

EUTHYROX is used to:

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

How does EUTHYROX work?

EUTHYROX contains levothyroxine sodium, which is a man-made type of thyroxine. Thyroxine is the hormone that is normally produced by the thyroid gland.

In hypothyroidism, the thyroid gland does not produce normal amounts of thyroxine. This causes levels of thyroid hormones in the blood to drop, which can cause changes in metabolism and the proper function of many organs. EUTHYROX helps to replace or supplement thyroxine in the body.

It may take a few weeks for EUTHYROX to begin working. Until it begins working, you may not notice any change in your symptoms.

Thyroid hormone replacement therapy is usually taken for life.

What are the ingredients in EUTHYROX?

Medicinal ingredients: Levothyroxine sodium

Non-medicinal ingredients: Corn starch, croscarmellose sodium, gelatin, lactose monohydrate and magnesium stearate. The following are the colour additives by tablet strength:

Strength	Colour Additive(s)
25 mcg	FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake
50 mcg	None
75 mcg	FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake
88 mcg	FD&C Yellow No. 5 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake
100 mcg	D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake
112 mcg	D&C Red No. 27 Aluminum Lake
125 mcg	FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 5 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake
137 mcg	FD&C Blue No. 1 Aluminum Lake
150 mcg	FD&C Blue No. 2 Aluminum Lake
175 mcg	FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 3 Aluminum Lake
200 mcg	D&C Red No. 30 Aluminum Lake
300 mcg	D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake

EUTHYROX comes in the following dosage forms:

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.

Do not use EUTHYROX if:

- you are allergic to levothyroxine sodium or to any of the other ingredients in EUTHYROX
- you have uncorrected adrenal insufficiency. This is a condition where your adrenal glands do not make enough of the hormone cortisol.
- you have pituitary insufficiency that has not been treated. This is a condition where the pituitary gland does not make enough of some hormones.
- you have thyrotoxicosis. This is a disease where the thyroid gland is overactive and produces too much thyroxine.
- you are pregnant and also using medicines to treat an overactive thyroid
- you have recently had a heart attack, or have myocarditis or pancarditis (inflammation of the heart or heart muscle)

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

- are pregnant or plan to become pregnant. This is because your dose will likely need to be increased.

- have any heart problems, whether or not you have received treatment for them. This includes a history of damage or diseased blood vessels of the heart (coronary artery disease and coronary insufficiency), heart failure, angina, hardening of the arteries or irregular heart rate.
- have other medical problems, whether or not you have received treatment for them, including:
    - high blood pressure
    - osteoporosis
    - blood clotting disorders
    - a history of thyroid, adrenal, or pituitary gland problems
- are a woman on long-term EUTHYROX therapy, especially post-menopausal women. This is because you may experience a decrease in bone mineral density.
- have one of the following rare hereditary conditions:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  This is because EUTHRYOX contains lactose.
- have a condition where your small intestine does not absorb enough nutrients from the food you eat. This is called a malabsorption syndrome.
- have signs or symptoms of psychotic disorders
- are switching from a different brand of levothyroxine sodium
- have myxedema coma, a medical emergency, which is a type of severe hypothyroidism

Other warnings you should know about:

Oral blood thinners: Taking EUTHYROX can affect how blood thinners work. If you are taking blood thinners by mouth (oral anticoagulant drugs) such as warfarin, the dose of these may need to be changed once you start taking EUTHYROX. Your healthcare professional will do blood tests from time to time to check how quickly your blood clots.

Diabetes: If you are receiving treatment for diabetes, the dose of your diabetes medication may need to be changed after starting EUTHYROX. Monitor sugar levels in your blood and urine as directed by your healthcare professional. Report any changes to your healthcare professional right away.

Adrenal insufficiency: If you have adrenal insufficiency you may be given other medications before you start EUTHYROX.

Surgery: Tell your healthcare professional about any surgery (including dental surgery) you are planning. Before the surgery, tell your dentist or surgeon that you are taking EUTHYROX.

Breast-feeding: Small amounts of thyroid hormones will pass into your breast milk. Regardless, you can continue to take EUTHYROX while you are breast-feeding. In fact, you should not stop your treatment, as normal levels of thyroid hormones will help maintain milk production.

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 for at least 2 days before you have a thyroid function test.

Driving and using machines: If EUTHYROX is used as directed, it is not expected to affect your ability to drive or use machines. Regardless, before performing such tasks, wait until you know how you respond to EUTHYROX.

Tests and check-ups:

- Before you start taking EUTHYROX your healthcare professional will check you for other conditions. This is to make sure that EUTHYROX is right for you.
- During your treatment you will need to have regular blood tests. These will be done to make sure you are receiving the correct dose. Based on the results of these blood tests, your dose of EUTHYROX may be changed.

  Adults: These tests may be done more often at the start of your treatment (about every 6 to 8 weeks). Eventually, you may only need these blood tests every 6 to 12 months. At a minimum, your healthcare professional should check your blood and do a physical exam once per year.

  Pregnant women: These tests will be done about every 4 weeks for the first half of your pregnancy and then at least once per week between weeks 26 and 32. You will also need a blood test about 6 weeks after your baby is born.

  Children:

  - These tests will be repeated regularly:
    - at 2 and 4 weeks after the start of treatment
    - 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 until the child stops growing
  - Blood tests and a physical exam should be done 2 weeks after any change in dose happens.
  - More frequent blood testing and check-ups may be needed depending on the child. Physical exams will also be done from time to time. These will include an assessment of how the child is growing.
  - To find out whether your child has permanent hypothyroidism, their dose may be lowered or their treatment stopped for about 30 days. This will happen when they are 3 years of age. Blood tests will be done during this time. Their treatment may or may not be restarted.

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 EUTHYROX:

- Nutritional supplements such as:
  - biotin (vitamin B7, vitamin H; including for hair and nail)
  - calcium carbonate
  - ferrous sulphate

    - vitamin B3 (niacin / nicotinic acid)
- Medicines to treat heart problems including high blood pressure such as:
    - digitalis glycosides (e.g. digoxin)
    - beta blockers like metoprolol, atenolol, bisoprolol, and propranolol
    - blood thinners like warfarin and heparin
    - amiodarone
    - diuretics like furosemide
    - nitroprusside
- Medicines to treat diabetes including insulin, tolbutamide or other medicines to lower blood sugar levels
- Medicines to treat digestion problems such as:
    - antacids that contain aluminum and magnesium (e.g. aluminum and magnesium hydroxides, simethicone)
    - proton pump inhibitors
    - sucralfate
    - metoclopramide
- Medicines used to lower high cholesterol such as:
    - cholestyramine
    - colestipol
    - lovastatin
- Medicines used to treat mental health problems and seizures such as:
    - antidepressants like sertraline, amitriptyline, maprotiline, St. John's Wort
    - phenobarbital
    - carbamazepine
    - lithium
    - diazepam
    - phenytoin
    - aminoglutethemide
    - methadone, heroin
    - hydantoins
    - perphenazine
- A medicine used to treat pain called ketamine
- Medicines to treat some cancers such as:
    - tyrosine kinase inhibitors like imatinib and sunitinib
    - octreotide
    - 5-flurouracil
    - Mitotane
    - Tamoxifen
    - Interleukin-2
    - Interferon-alpha
    - mercaptopurine
- Medicines used for weight lost including orlistat and other diet pills
- Medicines used to treat inflammatory conditions such as:

    - glucocorticoids (corticosteroids like dexamethasone and hydrocortisone)
    - non-steroidal anti-inflammatory drugs (NSAIDs) like fenamates, phenylbutazone and salicylates
- Other medicines to treat thyroid problems such as:
    - propylthiouracil (PTU)
    - methimazole
- Iodide, which is used for imaging like x-rays and CT scans
- Medicines for asthma or other breathing problems like theophylline and beta-sympatholytics / sympathomimetics (including salbutamol)
- Medicines to treat bacterial, viral or fungal infections such as:
    - medicines to treat HIV and AIDS including ritonavir, indinavir and lopinavir
    - medicines to treat tuberculosis such as para-aminosalicylate and ethionamide
    - ciprofloxacin
    - sulfonamides
    - rifampin
    - resorcinol
- A medicine to treat Parkinson's disease and restless leg syndrome called dopamine
- Medicines to lower levels of phosphorus in the blood such as:
    - sevelamer
- A medicine used to treat trouble sleeping called chloral hydrate
- Medicines used to treat malaria including:
    - chloroquinone
    - proguanil
- Hormones such as
    - estrogens that are taken by mouth including birth control pills
    - hormone replacement therapy
    - muscle building hormones including anabolic steroids
    - growth hormones such as somatropin

Eating certain foods like soybean flour (infant formula) and other soy containing products, cotton seed meal, walnuts, and dietary fiber may decrease the absorption of levothyroxine sodium. You may require a change in your dose.

Some medicines or supplements may interfere with blood tests done to measure thyroid hormone levels (called thyroid function tests). It is important to tell your healthcare professional of all medicines or supplements you are taking before and at the time of any blood test.

How to take EUTHYROX:

- Exactly as your healthcare professional tells you.
- Take your dose once per day at the same time each day on an empty stomach.
    - Adults and children: take the dose preferably 30 minutes to 1 hour before breakfast.
    - Infants: give the dose at least 30 minutes before the infant's first meal of the day.
- Swallow tablets whole with a glass of water.

- If your infant or child cannot swallow EUTHRYOX tablets whole, they can still take this medicine by following these steps:
    - Crush tablet(s) and mix the freshly crushed tablet(s) in about 5 to 10 mL (1 or 2 teaspoons) of water or a small amount of food like apple sauce. Do not mix the crushed tablets with foods or formula that contain large amounts of soybean, fibre, or iron.
    - Give this mixture to the child by spoon or dropper.
    - **Do not store the mixture for any period of time. Prepare a new mixture each time your child or infant needs to take their dose.**
- Food and drinks can affect how your body absorbs EUTHRYOX. For this reason, if you do take your dose with food or drinks, be sure to take it this way each time. You must be consistent with how you take your dose.
- If you are using other medicines, you should take your EUTHRYOX 4 hours before or 4 hours after these other medicines. Your healthcare professional can help you to establish when to take all of your medications.

Usual dose:

The usual dose of EUTHYROX 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
- the type of thyroid condition you have
- any other illness that you have (including if you are pregnant or have heart problems)
- if you are taking certain other medications
- how long you have had symptoms of thyroid problems
- how severe your symptoms are

You are likely to start at a lower dose. Your healthcare professional will adjust your dose based on your response to the medication. A child's dose will change as they grow and get older.

Use EUTHYROX only as prescribed by your healthcare professional. Do not change the amount you take or how often you take it, unless your healthcare professional tells you to. Like all medicines obtained from a healthcare professional, EUTHYROX must be used only by you and for the condition for which your healthcare professional has prescribed it. Do not stop taking EUTHYROX without first talking to your healthcare professional.

Overdose:

You may not experience symptoms of an overdose until several days after taking too much EUTHYROX.

Signs and symptoms of overdose may include: weight loss, increased appetite, heart palpitations (fast or irregular beating of the heart), nervousness, confusion, disorientation, diarrhea, abdominal cramps, sweating, fever, changes in period bleeding, convulsions, and seizures (fits). Blood clots in the brain, coma and death are also possible. If a large overdose occurs, additional treatment and measures from a healthcare professional will be needed.

If you think you, or a person you are caring for, have taken too much EUTHYROX, 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 of EUTHYROX, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and continue with your usual dosing schedule. Do not take 2 doses at the same time to make up for a missed dose. If you miss 2 or more doses in a row contact your healthcare professional.

What are possible side effects from using EUTHYROX?

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

- fever, flushing and excessive sweating
- trouble dealing with heat
- hyperactivity, irritability, restlessness, nervousness, anxiety, rapid changes in emotions
- trouble sleeping
- fatigue
- temporary hair loss
- diarrhea, vomiting, nausea, stomach cramps
- changes in period (menstrual cycle), trouble have a child (impaired fertility)
- headache
- shortness of breath
- muscle weakness, cramps, tremors
- reduced adult height due to early closure of growth plates in the bones of children

EUTHYROX can cause abnormal test results including liver function tests. Your healthcare professional will decide when to perform blood 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			✓
Serious allergic reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Osteoporosis (decrease in bone mineral density): back pain, loss of height over time, stooped posture, broken bones	✓		
Seizure (fits)**:** muscle twitching, changes in emotions, confusion, loss of consciousness with uncontrollable shaking			✓
Change in appetite, weight gain or loss	✓		
Slipped capital femoral epiphysis (a weakened hip joint in children): stiffness or pain in the knee or groin, walking with a limp, inability to bear weight on the affected side		✓	
Increased pressure in the brain (in children): headaches, vison 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.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 between 20°C to 25°C. Protect from light and moisture.

Keep out of reach and sight of children.

If you want more information about EUTHYROX:

- 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 at www.emdserono.ca, or by calling 1-888-737-6668.

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