

PRODUCT MONOGRAPH

Pr SYNTHROID®
levothyroxine sodium tablets, USP
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

Thyroid Hormone

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SYNTHROID®

levothyroxine sodium tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Tablet / 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.	Acacia, confectioner's sugar, lactose, magnesium stearate, povidone, talc and colour additives <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

SYNTHROID® (levothyroxine sodium tablets, USP) is indicated for:

- replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis;
Specific indications include: primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism.
- a pituitary TSH suppressant in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter, and in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

CONTRAINDICATIONS

SYNTHROID[®] (levothyroxine sodium tablets, USP) is contraindicated in:

- Patients with an apparent hypersensitivity to thyroid hormones or any of the inactive product constituents. For a complete listing of non-medicinal ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section. (Note: The 50 mcg tablet is formulated without colour additives for patients who are sensitive to dyes.) There is no well-documented evidence of true allergic or idiosyncratic reactions to thyroid hormone.
- Patients with untreated subclinical thyrotoxicosis (suppressed serum thyroid-stimulating hormone [TSH] with normal L-triiodothyronine/liothyronine [T₃] and L-thyroxine/levothyroxine [T₄] levels) or overt thyrotoxicosis of any etiology.
- Patients with acute myocardial infarction.
- Patients with uncorrected adrenal insufficiency, as thyroid hormones increase tissue demands for adrenocortical hormones and may thereby precipitate acute adrenal crisis. See **WARNINGS AND PRECAUTIONS**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

General

SYNTHROID[®] (levothyroxine sodium tablets, USP) 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 SYNTHROID[®] necessitating adjustments in dosing or monitoring of clinical or laboratory parameters to maintain therapeutic response. See **DRUG INTERACTIONS**.

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

It has been shown that differences in formulations of levothyroxine, despite an identical content of active ingredient, may be associated with differences in fractional gastrointestinal absorption. These differences may not be observed through measurement of total T₃ and T₄ serum levels. It is therefore recommended that patients who are switched from one levothyroxine formulation to another be re-titrated to the desired thyroid function. Accuracy in re-titration can best be achieved by using sensitive thyrotropin assays.

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

Lithium blocks the TSH-mediated release of T₄ and T₃. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual SYNTHROID[®] dose may be required.

Carcinogenesis and Mutagenesis

Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic T₄ is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid hormone therapy and breast cancer has not been confirmed and patients receiving SYNTHROID[®] for established indications should not discontinue therapy.

Cardiovascular

SYNTHROID[®] should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, and hypertension, and in the elderly who have a greater likelihood of occult cardiac disease. In these patients, levothyroxine sodium therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac diseases. See **WARNINGS AND PRECAUTIONS-Special Populations-Geriatrics** and **DOSAGE AND ADMINISTRATION**. If cardiac symptoms develop or worsen, the levothyroxine sodium dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Over-treatment with SYNTHROID[®] may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving levothyroxine sodium therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of thyroid hormone and sympathomimetic agents to patients with coronary artery disease may increase the risk of coronary insufficiency.

Endocrine and Metabolism

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

Patients treated concomitantly with SYNTHROID[®] and orlistat should be monitored for changes in thyroid function. See **DRUG INTERACTIONS**. Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism may involve a decreased absorption of iodine salts and/or levothyroxine.

Effects on Bone Mineral Density

In women, long-term levothyroxine therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in postmenopausal women on greater replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels. Therefore, it is recommended that patients receiving SYNTHROID[®] be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Patients with Nontoxic Diffuse Goiter or Nodular Thyroid Disease

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

Associated Endocrine Disorders

Hypothalamic/pituitary Hormone Deficiencies

In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated for adrenal insufficiency.

Autoimmune Polyglandular Syndrome

Use of SYNTHROID[®] in patients with concomitant diabetes mellitus, diabetes insipidus or adrenal cortical insufficiency may aggravate the intensity of their symptoms. Appropriate

adjustments of the various therapeutic measures directed at these concomitant endocrine diseases may therefore be required. Treatment of myxedema coma may require simultaneous administration of glucocorticoids. See **DOSAGE AND ADMINISTRATION**.

Hematologic

T₄ enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both SYNTHROID[®] and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly.

Psychiatric

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

Sexual Function/Reproduction

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

Special Populations

Pregnant Women

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

Thyroid hormones cross the placental barrier to some extent. T₄ levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of T₄ may not prevent *in utero* hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, preeclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. On the basis of current knowledge, SYNTHROID[®] should not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T₄ concentrations may decrease and TSH concentrations may increase to values outside normal ranges. As such, trimester-specific TSH reference values are recommended (See **DOSAGE & ADMINISTRATION – Administration – Pediatrics - Table 3**). Postpartum values are similar to preconception values. Elevations in TSH may occur as early as the fourth week gestation.

Pregnant women who are maintained on SYNTHROID[®] should have their TSH measured approximately every 4 weeks during the first half of pregnancy, and at least once between week 26 and 32, as levothyroxine dose adjustments are often required.

An elevated TSH should be corrected by an increase in levothyroxine sodium dose. After pregnancy, the dose can be decreased to the optimal preconception dose. A serum TSH level should be obtained approximately six weeks postpartum.

Nursing Women

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

Pediatrics (All ages including neonates)

Congenital hypothyroidism

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

Rapid restoration of normal serum T₄ concentrations is essential to prevent deleterious neonatal thyroid hormone deficiency effects on intelligence, overall growth, and development. Treatment should be initiated immediately upon diagnosis and generally maintained for life. The therapeutic goal is to maintain serum total T₄ or free T₄ (FT₄) in the upper half of the normal range and serum TSH in the normal range.

An initial starting dose of 10 to 15 mcg/kg/day (ages 0 to 3 months) will generally increase serum T₄ concentrations to the upper half of the normal range in less than 3 weeks. Clinical assessment of growth, development, and thyroid status should be monitored frequently. In most cases, the SYNTHROID[®] dose per body weight will decrease as the patient grows through infancy and childhood. See **DOSAGE AND ADMINISTRATION-Recommended Dose and Dosage Adjustment-Pediatric Dosage-Table 2**. Prolonged use of large doses in infants may be associated with temperament problems, which appear to be transient.

Thyroid function tests (serum total T₄ or FT₄, and TSH) should be monitored closely and used to determine the adequacy of levothyroxine sodium therapy. Serum T₄ normalization is usually followed by a rapid decline in TSH. Nevertheless, TSH normalization may lag behind T₄ normalization by 2 to 3 months or longer. The relative serum TSH elevation is more marked in the early months, but can persist to some degree throughout life. In rare patients TSH remains relatively elevated despite clinical euthyroidism and age-specific normal total T₄ or FT₄ levels. Increasing the levothyroxine sodium dosage to suppress TSH into the normal range may produce

overtreatment, with an elevated serum T₄ and clinical features of hyperthyroidism including: irritability, increased appetite with diarrhea, and sleeplessness. Another risk of prolonged overtreatment in infants is premature cranial synostosis.

Acquired hypothyroidism

The initial SYNTHROID[®] dose varies with age and body weight, and should be adjusted to maintain serum total T₄ or free T₄ levels in the upper half of the normal range. In general, unless there are overriding clinical concerns, children should be started on a full replacement dose. Children with underlying heart disease should be started at lower dosages, with careful upward titration. Children with severe, longstanding hypothyroidism may also be started on a lower initial dose followed by an upward titration, attempting to avoid premature epiphyseal closure. The recommended dose per body weight decreases with age. See **DOSAGE AND ADMINISTRATION-Recommended Dose and Dosage Adjustment-Pediatric Dosage-Table 2**.

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

If transient hypothyroidism is suspected hypothyroidism permanence may be assessed after the child reaches 3 years of age. Levothyroxine therapy may be interrupted for 30 days and serum T₄ and TSH measured. Low T₄ and elevated TSH confirm permanent hypothyroidism; therapy should be re-instituted. If T₄ and TSH remain in the normal range, a presumptive diagnosis of transient hypothyroidism can be made. In this instance, continued clinical monitoring and periodic thyroid function test re-evaluation may be warranted.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, an alternate approach is to reduce the replacement dose of SYNTHROID[®] 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, SYNTHROID[®] treatment should be discontinued for another 30-day trial period followed by repeat serum T₄ and TSH testing.

Geriatrics (> 50 years of age)

Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose. See **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**.

Monitoring and Laboratory Tests

Treatment of patients with SYNTHROID[®] requires periodic assessment of thyroid status by appropriate laboratory tests and clinical evaluation. Selection of appropriate tests for the diagnosis and management of thyroid disorders depends on patient variables such as presenting signs and symptoms, pregnancy, and concomitant medications. A measurement of free T₄ and TSH levels, using a sensitive TSH assay, is recommended to confirm a diagnosis of thyroid disease. Normal ranges for these parameters are age-specific in newborns and younger children.

TSH alone or initially may be useful for thyroid disease screening and for monitoring therapy for primary hypothyroidism as a linear inverse correlation exists between serum TSH and free T₄. Measurement of total serum T₄ and T₃, resin T₃ uptake, and free T₃ concentrations may also be useful. Antithyroid microsomal antibodies are an indicator of autoimmune thyroid disease. Positive microsomal antibody presence in an euthyroid patient is a major risk factor for the development of hypothyroidism. An elevated serum TSH in the presence of a normal T₄ may indicate subclinical hypothyroidism. Intracellular resistance to thyroid hormone is quite rare, and is suggested by clinical signs and symptoms of hypothyroidism in the presence of high serum T₄ levels. Adequacy of levothyroxine sodium therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring free T₄, which should be maintained in the upper half of the normal range. Measurement of TSH is not a reliable indicator of response to therapy for this condition. Adequacy of levothyroxine sodium therapy for congenital and acquired pediatric hypothyroidism should be assessed by measuring serum total T₄ or free T₄; these should be maintained in the upper half of the normal range. In congenital hypothyroidism, serum TSH normalization may lag behind serum T₄ normalization by 2 to 3 months or longer. In rare patients, serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal T₄ or free T₄ levels. See **WARNINGS AND PRECAUTIONS-Special Populations-Pediatrics**.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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

Post-Market Adverse Drug Reactions

Adverse reactions associated with SYNTHROID[®] are primarily those of hyperthyroidism due to therapeutic overdose. See **WARNINGS AND PRECAUTIONS** and **OVERDOSAGE**. They include the following:

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

Seizures have been reported rarely with the institution of levothyroxine sodium therapy.

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

DRUG INTERACTIONS

Overview

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

or elimination may alter the optimal therapeutic dose of SYNTHROID[®] (levothyroxine sodium tablets, USP).

Drug-Drug Interactions

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

The list of drug-thyroidal axis interactions in **Table 1** may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery or previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources (e.g., package inserts of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

Table 1. Drug-Thyroidal Axis Interactions

Drug or Drug Class	Effect
Drugs that may reduce TSH secretion - the reduction is not sustained; therefore, hypothyroidism does not occur	
Dopamine/Dopamine Agonists Glucocorticoids Octreotide	Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: dopamine (greater than or equal to 1 mcg/kg/min); glucocorticoids (hydrocortisone greater than or equal to 100 mg/day or equivalent); octreotide (greater than 100 mcg/day).
Drugs that alter thyroid hormone secretion	
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodide (including iodine-containing radiographic contrast agents) Lithium Thioamides - Methimazole - Propylthiouracil (PTU) - Carbimazole Sulfonamides Tolbutamide	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., 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. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T ₄ and T ₃ levels and increase TSH, although all values remain within normal limits in most patients.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing	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.,

Drug or Drug Class	Effect
radiographic contrast agents)	multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Drugs that may decrease T₄ absorption, which may result in hypothyroidism	
Antacids - Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Cation Exchange Resins - Sodium Polystyrene Sulfonate Ferrous Sulfate Orlistat Sucralfate	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least four (4) hours apart from these agents. Patients treated concomitantly with orlistat and levothyroxine should be monitored for changes in thyroid function.
Drugs that may alter T₄ and T₃ serum transport - but FT₄ concentration remains normal; and therefore, the patient remains euthyroid	
Drugs that may increase serum TBG Concentration	Drugs that may decrease serum TBG Concentration
Clofibrate Estrogen-containing Oral Contraceptives Estrogens (oral) Heroin/Methadone 5-Fluorouracil Mitotane Tamoxifen	Androgens/Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
Drugs that may cause protein-binding site replacement	
Furosemide (greater than 80 mg IV) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs - Fenamates	Administration of these agents with levothyroxine results in an initial transient increase in FT ₄ . Continued administration results in a decrease in Serum T ₄ and normal FT ₄ and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T ₄ and T ₃ to TBG and transthyretin. An initial increase in serum FT ₄ is followed by return of FT ₄ to normal levels with sustained therapeutic serum salicylate concentrations, although total T ₄ levels may decrease by as much as 30%.

Drug or Drug Class	Effect
- Phenylbutazone Salicylates (greater than 2 g/day)	
Drugs that may alter T₄ and T₃ metabolism	
Drugs that may increase hepatic metabolism, which may result in hypothyroidism	
Carbamazepine Hydantoins Phenobarbital Rifampin	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total and free T ₄ may be reduced by 20 to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.
Drugs that may decrease T₄ 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists - (e.g., propranolol greater than 160 mg/day) Glucocorticoids - (e.g., dexamethasone greater than or equal to 4 mg/day) Propylthiouracil (PTU)	Administration of these enzyme inhibitors decreases the peripheral conversion of T ₄ to T ₃ , leading to decreased T ₃ levels. However, serum T ₄ levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (greater than 160 mg/day), T ₃ and T ₄ levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T ₃ concentrations by 30% with minimal change in serum T ₄ levels. However, long-term glucocorticoid therapy may result in slightly decreased T ₃ and T ₄ levels due to decreased TBG production (see above).
Miscellaneous	
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.
Antidepressants - Tricyclics (e.g., amitriptyline) - Tetracyclics (e.g., maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., sertraline)	Concurrent use of tri/tetracyclic antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - Insulin	Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.

Drug or Drug Class	Effect
Cardiac glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.
Cytokines - Interferon-alpha - Interleukin-2	Therapy with interferon-alpha has been associated with the development of antithyroid microsomal antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients. Interferon-beta and -gamma have not been reported to cause thyroid dysfunction.
Growth Hormones - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators - (e.g., theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic agents	Thyroid hormones may reduce the uptake of ¹²³ I, ¹³¹ I, and ^{99m} Tc.
Sympathomimetics	Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Tyrosine Kinase Inhibitors	Plasma concentration of levothyroxine (thyroxine) possibly reduced by Tyrosine Kinase Inhibitors (e.g. imatinib, sunitinib).
Proton Pump Inhibitors	Plasma concentration of levothyroxine (thyroxine) possibly reduced by Proton Pump Inhibitors. Monitoring of TSH plasma level is recommended.
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.

TBG = thyroxine-binding globulin

Anticoagulants

Levothyroxine levels increase the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the levothyroxine sodium dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see **Table 1**).

Digitalis Glycosides

The therapeutic effects of digitalis glycosides may be reduced by SYNTHROID[®]. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see **Table 1**).

Orlistat

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

Drug-Food Interactions

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

Drug-Laboratory Interactions

A number of drugs or moieties are known to alter serum levels of TSH, T₄ and T₃ and may thereby influence the interpretation of laboratory tests of thyroid function. See **DRUG INTERACTIONS**.

1. Drugs such as estrogens and estrogen-containing oral contraceptives increase serum thyroxine-binding globulin (TBG) concentrations. TBG concentrations may also be increased during pregnancy, in infectious hepatitis and acute intermittent porphyria. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy. Familial hyper- or hypothyroxine-binding-globulinemias have been described. The incidence of TBG deficiency is approximately 1 in 9000. Certain drugs such as salicylates inhibit the

protein binding of T₄. In such cases, the unbound (free) hormone should be measured and/or determination of the free T₄ index (FT₄I) should be done.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage and rate of administration of SYNTHROID[®] (levothyroxine sodium tablets, USP) is determined by the indication, and must in every case be individualized according to patient response and laboratory findings.

Adult Dosage

Hypothyroidism

The goal of therapy for primary hypothyroidism is to achieve and maintain a clinical and biochemical euthyroid state with consequent resolution of hypothyroid signs and symptoms. The starting dose of SYNTHROID[®], the frequency of dose titration, and the optimal full replacement dose must be individualized for every patient, and will be influenced by such factors as age, weight, cardiovascular status, presence of other illness, and the severity and duration of hypothyroid symptoms.

In patients with hypothyroidism resulting from pituitary or hypothalamic disease, the possibility of secondary adrenal insufficiency should be considered, and if present, treated with glucocorticoids prior to initiation of SYNTHROID[®]. The adequacy of levothyroxine sodium therapy should be assessed in these patients by measuring FT₄, which should be maintained in the upper half of the normal range, in addition to clinical assessment. Measurement of TSH is not a reliable indicator of response to therapy for this condition.

TSH Suppression in Thyroid Cancer and Thyroid Nodules

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

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

Pediatric Dosage

Congenital or acquired hypothyroidism

The SYNTHROID[®] pediatric dosage varies with age and body weight. SYNTHROID[®] should be given at a dose that maintains T₄ or free T₄ in the upper half of the normal range and serum TSH in the normal range. See **WARNINGS AND PRECAUTIONS-Special Populations-Pediatrics**. Normalization of TSH may lag significantly behind T₄ in some infants. In general, despite the smaller body size of children, the dosage (on a weight basis) required to sustain full development and general thriving is higher than in adults (see **Table 2**).

Recommended Dose and Dosage Adjustment

Adult Dosage

Hypothyroidism

The usual full replacement dose of SYNTHROID[®] for younger, healthy adults is approximately 1.7 mcg/kg/day administered once daily. In the elderly, the full replacement dose may be altered by decreases in T₄ metabolism and levothyroxine sodium absorption. Older patients may require less than 1 mcg/kg/day. Children generally require higher doses. See **Pediatric Dosage**. Women who are maintained on SYNTHROID[®] during pregnancy may require increased doses. See **WARNINGS AND PRECAUTIONS-Special Populations-Pregnant Women**.

Therapy is usually initiated in younger, healthy adults at the anticipated full replacement dose. Clinical and laboratory evaluations should be performed at 6 to 8 week intervals (2 to 3 weeks in severely hypothyroid patients), and the dosage adjusted by 12.5 to 25 mcg increments until the serum TSH concentration is normalized and signs and symptoms resolve. For most patients older than 50 years and for patients under 50 years of age with a history of/ underlying cardiac disease, an initial starting dose of 25 to 50 mcg/day of SYNTHROID[®] is recommended, with gradual increments in dose at six to eight week intervals, as needed. The recommended starting dose of SYNTHROID[®] in elderly patients with cardiac disease is 12.5 to 25 mcg/day, with gradual dose increments at four to six week intervals. If cardiac symptoms develop or worsen, the cardiac disease should be evaluated and the dose of levothyroxine sodium reduced. Rarely, worsening angina or other signs of cardiac ischemia may prevent achieving a TSH in the normal range.

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

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

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

Myxedema Coma

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

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

TSH Suppression in Thyroid Cancer and Thyroid Nodules

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

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

Pediatric Dosage

Congenital or acquired hypothyroidism

Therapy is usually initiated at the full replacement dose (see **Table 2**). Infants and neonates with very low (< 5 mcg/dL) or undetectable serum T₄ levels should be started at higher end of the dosage range (e.g., 50 mcg daily). A lower dose (e.g., 25 mcg daily) should be considered for neonates at risk of cardiac failure, increasing every few days until a full maintenance dose is reached. In children with severe, longstanding hypothyroidism or pre-existing cardiac insufficiency, SYNTHROID[®] should be initiated gradually, with an initial 25 mcg dose for two weeks, then increasing by 25 mcg every 2 to 4 weeks until the desired dose, based on serum T₄ and TSH levels, is achieved. See **WARNINGS AND PRECAUTIONS-Special Populations-Pediatrics**.

Table 2. Dosage Guidelines for Pediatric Hypothyroidism

Age	Daily dose (mcg) per kg of body weight *
0 - 3 months	10 – 15
3 - 6 months	8 – 10
6 - 12 months	6 – 8
1 - 5 years	5 – 6
6 - 12 years	4 – 5
> 12 years but growth and puberty incomplete	2 – 3
Growth and puberty complete	1.6– 1.7

* To be adjusted on the basis of clinical response and laboratory tests. See **WARNINGS AND PRECAUTIONS-Special Populations-Pediatrics**.

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

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

Evaluation at more frequent intervals is indicated when compliance is questioned or abnormal laboratory values are obtained. Patient evaluation is also advisable approximately 2 to 4 weeks after any change in SYNTHROID[®] dose.

Missed Dose

A missed dose of one tablet can be taken with the next dose. If more than 2 tablets are missed, the patient should consult with their doctor.

Administration

Pediatrics

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

Table 3 summarizes the **DOSAGE AND ADMINISTRATION** of SYNTHROID[®].

Table 3. 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	4-6 weeks*	Free T ₄ level in upper half of normal range
Congenital/Acquired Hypothyroidism	Infants/Children	See Table 2	25 mcg/day	1-2 months (until 1 year), 2-3 months (until 3 years), 3-12 months 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 weeks*	T ₄ level in upper half of normal range, normal TSH
Severe Congenital Hypothyroidism (T ₄ < 5 mcg/dL)	Neonate	50 mcg/day	25 mcg/day	2-4 weeks*	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 weeks	Normal TSH (age-specific reference range)
Hypothyroidism	Adults <50 years	1.7 mcg/kg/day	25-50 mcg/day	6-8 weeks	Normal TSH (between 0.5 and 2.0 mU/L)
	Adults >50 years	25-50 mcg/day	12.5-25 mcg/day	6-8 weeks	

Hypothyroidism with Cardiac Disease	Adults <50 years	25-50 mcg/day	12.5-25 mcg/day	6-8 weeks	Normal TSH (between 0.5 and 2.0 mU/L)
	Adults >50 years	12.5-25 mcg/day	12.5-25 mcg/day	4-6 weeks	
Severe Hypothyroidism	Adults < 50 years	12.5-25 mcg/day	25 mcg/day	2-4 weeks	Normal TSH (between 0.5 and 2.0 mU/L)
	Infants/Children	25 mcg/day	25 mcg/day	2-4 weeks	Normal TSH (age-specific reference range)
Hypothyroidism (short period) or Recently Treated with Hyperthyroidism	Adults > 50 years	< 1.7 mcg/kg/day	25-50 mcg/day	6-8 weeks	Normal TSH (between 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	Every 4 weeks during first half of pregnancy; at least once between week 26 and 32; approximately 6 weeks postpartum	Normal TSH (trimester-specific) and FT4 in the upper third of normal range 1st trimester: < 2.5 mU/L 2nd trimester: < 3.0 mU/L 3rd trimester: < 3.5 mU/L
Secondary Hypothyroidism	Not Specified	**	**	**	Free T4 level in upper third of normal range
Tertiary Hypothyroidism	Not Specified	**	**	**	Free T4 level in upper third of normal range
Subclinical Hypothyroidism	Not Specified	25-50 mcg/day	Adjust as necessary	6-8 weeks	Normal TSH (between 0.5 and 2.0 mU/L)
Well-differentiated (papillary or follicular) Thyroid Cancers	Not Specified	> 2 mcg/kg/day	25-50 mcg/day	6-8 weeks	TSH < 0.1 mU/L TSH < 0.01 mU/L for patients with high risk tumors
Benign Nodules and Nontoxic Multinodular Goiter	Not Specified	1.7-2 mcg/kg/day (Suppression not < 0.1 mU/L)	25-50 mcg/day	6-8 weeks	TSH 0.1 – 0.3 mU/L for nodules and for multinodular goiter

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

*For Congenital Hypothyroidism, the current guidelines recommend a 2 week monitoring interval at the beginning of therapy until normalization of TSH levels

OVERDOSAGE

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

Signs and Symptoms

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

Treatment of Overdosage

SYNTHROID[®] should be reduced in dose or temporarily discontinued if signs and symptoms of overdose appear.

In the treatment of acute massive SYNTHROID[®] overdose, symptomatic and supportive therapy should be instituted immediately. Treatment is aimed at reducing gastrointestinal absorption and counteracting central and peripheral effects, mainly those of increased sympathetic activity. The stomach should be emptied immediately by emesis or gastric lavage if not otherwise contraindicated (e.g., by coma, convulsions or loss of gag reflex). Cholestyramine and activated charcoal have also been used to decrease levothyroxine sodium absorption. Beta-receptor antagonists, particularly propranolol, are useful in counteracting many of the effects of increased central and peripheral sympathetic activity, especially when no contraindications exist for its use. Provide respiratory support as needed; control congestive heart failure and arrhythmia, control fever, hypoglycemia, and fluid loss as necessary. Large doses of antithyroid drugs (e.g., methimazole, carbimazole, or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones. Cardiac glycosides may be administered if congestive heart failure develops. Glucocorticoids may be administered to inhibit the conversion of T₄ to T₃. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Since T₄ is extensively protein bound, very little drug will be removed by dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The synthesis and secretion of the major thyroid hormones, T₃ and T₄, from the normally functioning thyroid gland are regulated by complex feedback mechanisms of the hypothalamic-pituitary-thyroid axis. The thyroid gland is stimulated to secrete thyroid hormones by the action of thyrotropin (thyroid stimulating hormone, TSH), which is produced in the anterior pituitary gland. TSH secretion is in turn controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus, circulating thyroid hormones, and possibly other mechanisms. Thyroid hormones circulating in the blood act as feedback inhibitors of both TSH and TRH secretion. Thus, when serum concentrations of T₃ and T₄ are increased, secretion of TSH and TRH decreases. Conversely, when serum thyroid hormone concentrations are decreased, secretion of TSH and TRH is increased. Administration of exogenous thyroid hormones to euthyroid individuals results in suppression of endogenous thyroid hormone secretion.

The mechanisms by which thyroid hormones exert their physiologic actions have not been completely elucidated, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T₃ and T₄ are transported into cells by passive and active mechanisms. T₃ in cell cytoplasm and T₃ generated from T₄ within the cell diffuse into the nucleus and bind to thyroid receptor proteins, which appear to be primarily attached to DNA. Receptor binding leads to activation or repression of DNA transcription, thereby altering the amounts of mRNA and resultant proteins. Changes in protein concentrations are responsible for the metabolic changes observed in organs and tissues.

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

The physiologic effects of thyroid hormones are produced primarily by T₃, a large portion of which (approximately 80%) is derived from the deiodination of T₄ in peripheral tissues. About 70 to 90 percent of peripheral T₃ is produced by monodeiodination of T₄ at the 5 position (outer ring). Peripheral monodeiodination of T₄ at the 5 position (inner ring) results in the formation of reverse triiodothyronine (rT₃), which is calorically inactive.

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

Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, Hashimoto's thyroiditis, multinodular goiter and, as adjunctive therapy in the management of thyrotropin-

dependent well-differentiated thyroid cancer. See **INDICATIONS AND CLINICAL USE**, **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**.

Pharmacokinetics

Absorption

Few clinical studies have evaluated the kinetics of orally administered thyroid hormone. In animals, the most active sites of absorption appear to be the proximal and mid-jejunum. T₄ is not absorbed from the stomach and little, if any, drug is absorbed from the duodenum. There seems to be no absorption of T₄ from the distal colon in animals. A number of human studies have confirmed the importance of an intact jejunum and ileum for T₄ absorption and have shown some absorption from the duodenum. Studies involving radioiodinated T₄ fecal tracer excretion methods, equilibration, and AUC methods have shown that absorption varies from 48 to 80 percent of the administered dose. The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes, such as sprue. Absorption may also decrease with age. The degree of T₄ absorption is dependent on the product formulation as well as on the character of the intestinal contents, the intestinal flora, including plasma protein and soluble dietary factors, which bind thyroid hormone, making it unavailable for diffusion. Decreased absorption may result from administration of infant soybean formula, ferrous sulfate, sodium polystyrene sulfonate, aluminum hydroxide, sucralfate, or bile acid sequestrants. T₄ absorption following intramuscular administration is variable. The relative bioavailability of SYNTHROID[®] (levothyroxine sodium, USP) tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%.

Distribution

Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated. More than 99% of circulating hormones is bound to serum proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA). T₄ is more extensively and firmly bound to serum proteins than is T₃. Only unbound thyroid hormone is metabolically active. The higher affinity of TBG and TBPA for T₄ partly explains the higher serum levels, slower metabolic clearance, and longer serum elimination half-life of this hormone.

Certain drugs and physiologic conditions can alter the binding of thyroid hormones to serum proteins and/or the concentrations of the serum proteins available for thyroid hormone binding. These effects must be considered when interpreting the results of thyroid function tests. See **(WARNINGS AND PRECAUTIONS-Monitoring and Laboratory Tests)** and **(DRUG INTERACTIONS)**

Metabolism

The liver is the major site of degradation for both hormones. T₃ and T₄ are conjugated with glucuronic and sulfuric acids and excreted in the bile. There is an enterohepatic circulation of

thyroid hormones, as they are liberated by hydrolysis in the intestine and reabsorbed. A portion of the conjugated material reaches the colon unchanged, is hydrolyzed there, and is eliminated as free compounds in the feces. In man, approximately 20 to 40 percent of T₄ is eliminated in the stool. About 70 percent of the T₄ secreted daily is deiodinated to yield equal amounts of T₃ and rT₃. Subsequent deiodination of T₃ and rT₃ yields multiple forms of diiodothyronine. A number of other minor T₄ metabolites have also been identified. Although some of these metabolites have biologic activity, their overall contribution to the therapeutic effect of T₄ is minimal.

Excretion

Thyroid hormones are primarily eliminated by the kidneys. T₄ is eliminated slowly from the body (see **Table 4**), with a half-life of 6 to 7 days. T₃ has a half-life of 1 to 2 days.

Table 4. Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	t _{1/2} (days)	Protein Binding (%) ²
Levothyroxine, T ₄	10 to 20	1	6 to 7 ¹	99.96
Liothyronine, T ₃	1	4	≤ 2	99.5

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

2 Includes TBG, TBPA, and TBA

STORAGE AND STABILITY

Store at controlled room temperature 15 to 25°C (59 to 77°F). SYNTHROID[®] (levothyroxine sodium tablets, USP) should be protected from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SYNTHROID[®] (levothyroxine sodium tablets, USP): round, colour coded, scored tablet debossed with “SYNTHROID” on one side and potency on the other side. SYNTHROID[®] (levothyroxine sodium tablets, USP) contains the following inactive ingredients: acacia, confectioner's sugar, lactose, magnesium stearate, povidone and talc.

Gluten-free. Each tablet contains less than 70 mg of lactose.

The strengths available and the colour additives by tablet strength are as follows (see **Table 5**):

Table 5. SYNTHROID® Tablet Characteristics

Strength (mcg)	Tablet Colour	Colour Additive(s)
25	Orange	FD&C Yellow No. 6
50	White	None
75	Violet	FD&C Red No. 40 FD&C Blue No. 2
88	Olive	FD&C Blue No. 1 FD&C Yellow No. 6 D&C Yellow No. 10
100	Yellow	D&C Yellow No. 10 FD&C Yellow No. 6
112	Rose	D&C Red No. 27 & 30
125	Brown	FD&C Yellow No. 6 FD&C Red No. 40 FD&C Blue No. 1
137	Turquoise	FD&C Blue No. 1
150	Blue	FD&C Blue No. 2
175	Lilac	FD&C Blue No. 1 D&C Red. No. 27 & 30
200	Pink	FD&C Red No. 40
300	Green	D&C Yellow No. 10 FD&C Yellow No. 6 FD&C Blue No. 1

Meets USP Dissolution Test 3.

All SYNTHROID® strengths are available in bottles of 90 tablets each; SYNTHROID® 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300 mcg strengths are also available in bottles of 1000 tablets each.

PART II: SCIENTIFIC INFORMATION

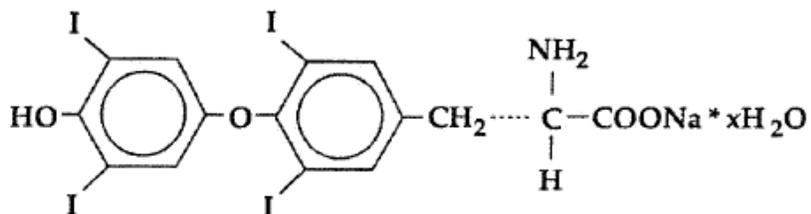
PHARMACEUTICAL INFORMATION

Proper name: Levothyroxine sodium

Chemical name: L-3,3',5,5'-tetraiodothyronine sodium salt

Molecular formula $C_{15}H_{10}I_4N NaO_4 \cdot H_2O$ 798.86 g/mol (anhydrous)
and molecular
mass:

Structural formula:



Physicochemical Levothyroxine sodium occurs as a light yellow to buff-coloured,
properties: odourless, tasteless, hygroscopic powder. Levothyroxine sodium is
very slightly soluble in water and slightly soluble in alcohol.

CLINICAL TRIALS

The published studies presented in this section support the effectiveness of SYNTHROID[®] (levothyroxine sodium tablets, USP) in the treatment of hypothyroidism. They are considered to have at least some of the characteristics of adequate and well-controlled as defined under ICH Good Clinical Practice. The controlled clinical studies are primarily: 1) studies that investigated the biochemical response to SYNTHROID[®] of patients with hypothyroidism and the correlation of the optimal clinical dose with the pathology of hypothyroidism, 2) conventional studies of untreated hypothyroid patients or those switched from another brand of the same active drug, and 3) studies that analyze the dose-response characteristics in hypothyroid patients replaced with SYNTHROID[®] or patients receiving SYNTHROID[®] for suppression of TSH. In all cases, objective biochemical endpoints (e.g., TSH, T₄, etc.), which minimize the potential for influence of chance or bias on results, were used to assess the effectiveness of SYNTHROID[®] as replacement or suppressive therapy. The results of the studies demonstrate that with careful dose titration to an objective, biochemical endpoint, SYNTHROID[®] is effective both for initial and maintenance therapy of hypothyroid adults. On the whole, the average L-thyroxine replacement doses reported in these studies are in close agreement with each other and average replacement doses reported in the literature and recommended by thyroid experts.

Study Demographics and Trial Design

Table 6. Summary of Patient Demographics for Clinical Trials in Specific Indication

Author / Manuscript Title	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)	Gender (M/F)
Kabadi UM., 1994/ "Optimal L-thyroxine dose in primary hypothyroidism".	Longitudinal	25-200 mcg/day Oral dosage form	186	NR (25-84 years)	152/34
Kabadi UM., 1989/ "Optimal L-thyroxine dose in hypothyroidism".	Longitudinal	50-200 mcg/day Oral dosage form	156*	NR (25-84 years)	133/23
Kabadi UM, Jackson T., 1995/ "TSH predictor in hypothyroidism".	Longitudinal	25-225 mcg/day Oral dosage form	192	NR (25-84 years)	171/21
Hennessey J, et al., 1985/ "Equivalency of two L-thyroxine preparations".	Crossover	50-200 mcg/day Oral dosage form	34	NR	NR
Fish LH, et al., 1987/ "Replacement dose in hypothyroidism".	Longitudinal	25-150 mcg/day Oral dosage form	19	NR	NR

Author / Manuscript Title	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)	Gender (M/F)
Ain KG, et al., 1996/ "Effects of restrictive formulary".	Longitudinal	Restricted arm (n=87): 1.9 ± 0.1 mcg/kg/day Non-restricted arm (n=148): 2.0 ± 0.1 mcg/kg/day Oral dosage form	241	Restricted arm: (n=89): 39.3 ± 2.4 year (range NR) Non-restricted arm (n=152): 44.2 ± 1.3 year (range NR)	74/167
Ain KG, et al., 1993/ "TFTs affected by time of blood sampling".	Longitudinal	150-200 mcg/day Oral dosage form	51	NR	NR
Sherman SI, et al., 1997/ "Effects of T ₃ compared to T ₄ ".	Longitudinal	2.2 – 2.6 mcg/kg/day (LT ₄ -only arm) Oral dosage form	11 (LT ₄ -only arm)	NR	NR
Liu X-Q, et al., 1998/ "Effects of L-thyroxine on serum lipoproteins".	Longitudinal	183 (mean) Oral dosage form	10	45.7 ± 10.6 year (range NR)	2/8
Hussein W, et al., 1999/ "Effects of L-thyroxine on serum homocysteine".	Longitudinal	NR	14	45.7 (25 – 77 yr)	4/10

* This is considered to be an earlier publication of the same patient population presented in Kabadi, 1994. The 156 patients described are not added into the total number of patients.

NR = not reported

LT₄ = L-thyroxine

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PART III: CONSUMER INFORMATION

Pr **SYNTHROID[®]**
levothyroxine sodium tablets, USP

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

ABOUT THIS MEDICATION

What the medication is used for:

- SYNTHROID[®] is used when the thyroid gland does not produce enough hormone (hypothyroidism). It is also used to help decrease the size of enlarged thyroid glands (known as goiter) and to treat thyroid cancer.

What it does:

SYNTHROID[®] contains levothyroxine sodium, the same as the thyroxine hormone, produced by the normally functioning thyroid gland.

The thyroid gland produces and releases two hormones: thyroxine and liothyronine. In other areas of the body, thyroxine is changed into liothyronine, which is a more active form of thyroid hormone. These hormones are responsible for maintaining a normal rate of metabolism in the body.

When the thyroid gland is unable to produce normal amounts of thyroxine, the level of thyroid hormones in the blood decreases (hypothyroidism). This results in a reduced rate of metabolism.

Levothyroxine sodium in SYNTHROID[®] is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient (temporary) hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis). Low levels of thyroid hormone interfere with the proper function of many organs and affect metabolism.

When it should not be used:

SYNTHROID[®] should not be used in patients with:

- any unusual or allergic reaction to thyroid hormones or any of the inactive ingredients;
- overactive thyroid gland (thyrotoxicosis) of any cause;
- uncorrected adrenal gland under-activity.

What the medicinal ingredient is:

Levothyroxine sodium USP

What the important non-medicinal ingredients are:

Acacia, confectioner's sugar, lactose, magnesium stearate, povidone, talc and colour additives.

For a full listing of non-medicinal ingredients see PART I of the Product Monograph.

What dosage forms it comes in:

SYNTHROID[®] comes as tablets in the following strengths:

25 mcg (List No. 04341), 50 mcg (List No. 04552), 75 mcg (List No. 05182), 88 mcg (List No. 06594), 100 mcg (List No. 06624), 112 mcg (List No. 09296), 125 mcg (List No. 07068), 137 mcg (List No. 03727), 150 mcg (List No. 07069), 175 mcg (List No. 07070), 200 mcg (List No. 07148), and 300 mcg (List No. 07149).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Thyroid hormones, including SYNTHROID[®], either alone or with other medicines, should not be used for the treatment of obesity or for weight loss as they could produce serious or even life threatening side effects.

BEFORE or WHILE you use SYNTHROID[®] talk to your doctor or pharmacist if:

- you are allergic to any foods or medication;
- you are pregnant or intend to become pregnant, or are breast-feeding. If you become pregnant while taking SYNTHROID[®], your dose of SYNTHROID[®] will likely have to be increased;
- you have any heart problem, whether or not you have received treatment for them (especially history of heart attack, heart disease, hardening of the arteries);
- you have other medical problems, whether or not you have received treatment for them (especially high blood pressure, osteoporosis, blood clotting disorder, or history of thyroid, adrenal and/or pituitary gland problems);
- you have diabetes. Your dose of insulin or oral anti-diabetic agent may need to be changed after starting SYNTHROID[®]. You should monitor your blood and urinary sugar levels as directed by your doctor and report any changes to your doctor immediately;
- you have signs or symptoms of psychotic disorders;
- you are taking an oral anticoagulant (blood thinner) such as warfarin. Your dose may need to be changed after starting SYNTHROID[®];

- you are taking any other medications (prescription or over-the-counter);
- you are planning to have any kind of surgery (including dental surgery) or emergency treatment. You should inform your doctor or dentist that you are taking SYNTHROID® before having any kind of surgery;
- your brand of levothyroxine was changed;
- you are a woman on long-term therapy. You may experience decrease in bone density;
- you have any allergies to this drug or its ingredients or components of the container;
- you are taking orlistat.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with SYNTHROID® includes but are not limited to the following:

- digitalis glycosides (e.g. digoxin)
- anti-diabetic agents (insulin or oral hypoglycemic drugs)
- glucocorticoids (corticosteroids e.g., dexamethasone, prednisone)
- antacids containing aluminium and magnesium (e.g. aluminium and magnesium hydroxides, simethicone)
- calcium carbonate
- diazepam (e.g., Valium®)
- ferrous sulphate
- antidepressants
- lithium
- iodide
- anticoagulants (blood thinners e.g., warfarin)
- appetite suppressants (diet pills)
- beta blockers (e.g., propranolol, atenolol, metoprolol)
- cholestyramine (e.g., Olestyr®)
- colestipol (e.g., Colestid®)
- medicines for asthma or other breathing problems
- medicines for colds, sinus problems, hay fever or other allergies (including nose drops or sprays)
- orlistat (e.g., Xenical®)
- tyrosine kinase inhibitors (e.g., imatinib, sunitinib).
- proton pump inhibitors

Some medicines may interfere with any blood tests done to determine thyroid hormone levels (thyroid function tests). It is important to inform your doctor of all medicines you are taking before and at the time of blood tests.

Eating certain foods such as soybean flour, soybean infant formula, cotton seed, walnuts and dietary fiber may decrease absorption of levothyroxine. You may require a change in the dose.

PROPER USE OF THIS MEDICATION

Use SYNTHROID® only as prescribed by your doctor. Thyroid hormone replacement is usually taken for life. Do not change the amount you take or how often you take it, unless directed to do so by your doctor. Like all medicines obtained from your doctor,

SYNTHROID® must be used only by you and for the condition determined appropriate by your doctor. Do not stop taking levothyroxine sodium without talking to your doctor.

Take SYNTHROID® as a single dose, preferably on an empty stomach, one half to one hour before breakfast. SYNTHROID® should be taken with a full glass of water. As food and drink can significantly change the absorption of SYNTHROID®, you are advised to take SYNTHROID® at the same time every day and be consistent in how you take it with regards to meals [i.e. either always take it on an empty stomach (preferred method) or take it with food]. Levothyroxine sodium absorption is increased on an empty stomach.

Usual dose:

The dose of these medicines will be different for different patients. *Follow your doctor's orders or the directions on the label.*

Treatment is usually started with lower doses that are increased a little at a time to prevent side effects.

Adults and children (>12 years): Therapy is usually initiated at the anticipated full replacement dose. The dosage is adjusted by 12.5 to 25 mcg increments.

Patients older than 50 years or patients younger than 50 years with a history of cardiovascular disease: The starting dose should be 25 to 50 mcg once daily with adjustments every 6 to 8 weeks as needed.

Elderly patients with cardiac disease: The recommended starting dose is 12.5 to 25 mcg/day, with gradual dose increments at 4 to 6 week intervals.

Overdose:

If you or someone you know accidentally takes more than the prescribed dose, contact your doctor immediately or go to the nearest hospital with the tablets. Tell your doctor or hospital how much was taken. Treat even small overdoses seriously.

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

Missed Dose:

If you forget to take one tablet, take another as soon as you remember, unless it is almost time for your next dose. If it is, take the dose you missed with your next dose.

If you miss 2 or more doses in a row or if you have any questions about this, check with your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

SYNTHROID[®] can cause some side effects. They include:

- chest pain
- fast or irregular heart beat
- weight loss or gain
- sweating
- nervousness
- temporary hair loss
- decrease of bone mineral density
- diarrhea
- vomiting

HOW TO STORE IT

Keep SYNTHROID[®] and all other medicines out of reach of children.

SYNTHROID[®] tablets should be stored at room temperature (15 to 25° C or 59 to 77° F) protected from light and moisture.

Do not take your tablets after the expiry date shown on the label.

It is important to keep the SYNTHROID[®] tablets in the original package.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

The most recent version of this document plus the full Product Monograph, prepared for health professionals can be found at:

www.mylan.ca

or by contacting the sponsor, BGP Pharma ULC, Etobicoke, Ontario, M8Z 2S6 at:

1-844-596-9526

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