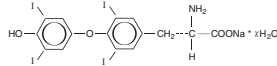


LEVOXYL® (levothyroxine sodium, USP)

FOR ORAL ADMINISTRATION

Inactive Ingredients

Microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The following are the coloring additives per tablet strength:



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

CLINICAL PHARMACOLOGY

Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates secretion of thyroid-stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyronine (T₁) 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 physiologic 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, at doses individualized according to patient response, is effective as replacement or supplementary 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 USAGE, PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Pharmacokinetics

Absorption – Absorption of orally administered T₄ from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of LEVOXYL® tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 98%. 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 **PRECAUTIONS, Drug Interactions and Drug-Food Interactions**).

Distribution – Circulating thyroid hormones are greater than 99% bound to plasma proteins, including 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 T₄ partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T₄ compared to T₃. 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 **PRECAUTIONS, Drug Interactions and Drug-Laboratory Test Interactions**). Thyroid hormones do not readily cross the placental barrier (see **PRECAUTIONS, Pregnancy**).

Metabolism – T₄ is slowly eliminated (see **TABLE 1**). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T₄ is derived from peripheral T₄ by monodeiodination. The liver is the major site of degradation for both T₄ and T₃, with T₄ deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T₄ is deiodinated to yield equal amounts of T₃ and reverse T₃ (rT₃). T₃ and rT₃ 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 – Thyroid hormones are primarily eliminated by the kidneys. 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.

Table 1: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	1/2 ^{elim}	Protein Binding (%) ¹
Levothyroxine (T ₄)	10–20	1	6–7 ²	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

INDICATIONS AND USAGE

Levothyroxine sodium is used for the following indications:

Hypothyroidism – As 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 and subclinical hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total congenital absence of the thyroid gland, or from the effects of surgery, radiation, or drugs, with or without the presence of goiter.

Pituitary TSH Suppression – In the treatment or prevention of various types of euthyroid goiters (see **WARNINGS and PRECAUTIONS**), including thyroid nodules (see **WARNINGS and PRECAUTIONS**), subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter (see **WARNINGS and PRECAUTIONS**) and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

CONTRAINDICATIONS

Levothyroxine is contraindicated in patients with untreated subclinical (suppressed serum TSH level with normal T₃ and T₄ levels) or overt thyrotoxicosis of any etiology and in patients with acute myocardial infarction. Levothyroxine is contraindicated in patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see **PRECAUTIONS**). LEVOXYL® is contraindicated in patients with hypersensitivity to any of the inactive ingredients in LEVOXYL® tablets (see **DESCRIPTION, Inactive Ingredients**).

WARNINGS

WARNING: Thyroid hormones, including LEVOXYL®, 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.

Levothyroxine sodium should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

In patients with nontoxic diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine sodium therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitating overt thyrotoxicosis (see **CONTRAINDICATIONS**). If the serum TSH level is not suppressed, LEVOXYL® 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.

PRECAUTIONS

General

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

Effects on bone mineral density – In women, long-term levothyroxine sodium therapy has been associated with decreased bone mineral density, especially in postmenopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Patients with underlying cardiovascular disease – Exercise caution when administering levothyroxine to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see **WARNINGS, PRECAUTIONS, Geriatric Use; and DOSAGE AND ADMINISTRATION**). If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Patients with nontoxic diffuse goiter or nodular thyroid disease – Exercise caution when administering levothyroxine to patients with nontoxic diffuse goiter or nodular thyroid disease in order to prevent precipitation of thyrotoxicosis (see **WARNINGS**). If the serum TSH is already suppressed, levothyroxine sodium should not be administered (see **Contraindications**).

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 (see **PRECAUTIONS, Autoimmune polyglandular syndrome**) for adrenal insufficiency.

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

Other associated medical conditions

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.

Information for Patients

Patients should be informed of the following information to aid in the safe and effective use of LEVOXYL®:

1. Notify your physician if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding or are taking any other medications, including prescription and over-the-counter preparations.
2. Notify your physician of any other medical conditions you may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems. Your dose of medications used to control these other conditions may need to be adjusted while you are taking LEVOXYL®. If you have diabetes, monitor your blood and/or urinary glucose levels as directed by your physician and immediately report any changes to your physician. If you are taking anticoagulants (blood thinners), your clotting status should be checked frequently.
3. Use LEVOXYL® only as prescribed by your physician. Do not discontinue or change the amount you take or how often you take it, unless directed to do so by your physician.
4. The levothyroxine in LEVOXYL® 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 hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis).
5. Take LEVOXYL® in the morning on an empty stomach, at least one-half hour before eating any food.
6. LEVOXYL® may rapidly swell and disintegrate resulting in choking, gagging, the tablet getting stuck in your throat or difficulty swallowing. It is very important that you take the tablet with a full glass of water. Most of these problems disappeared when Levoxy® tablets were taken with water.
7. It may take several weeks before you notice an improvement in your symptoms.
8. Notify your physician if you experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.
9. Notify your physician if you become pregnant while taking LEVOXYL®. It is likely that your dose of LEVOXYL® will need to be increased while you are pregnant.
10. Notify your physician or dentist that you are taking LEVOXYL® prior to any surgery.
11. Partial hair loss may occur rarely during the first few months of LEVOXYL® therapy, but this is usually temporary.
12. LEVOXYL® should not be used as a primary or adjunctive therapy in a weight control program.
13. Keep LEVOXYL® out of the reach of children. Store LEVOXYL® away from heat, moisture, and light.

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 **PRECAUTIONS, Drug Interactions and Drug-Laboratory Test Interactions**). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of LEVOXYL® may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T₄ potency of the drug product.

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 dose titration depends on the clinical situation but it is generally recommended at 6–8 week intervals until normalization. For patients who have recently initiated levothyroxine therapy and whose serum TSH is normalized, or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured after 8–12 weeks. 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 LEVOXYL® (see **WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION**).

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 LEVOXYL® therapy and/or of the serum TSH to decrease below 20 mIU/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 LEVOXYL®.

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 LEVOXYL® dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals (see **PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION**).

Secondary (pituitary and tertiary, hypothalamic) hypothyroidism

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

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 LEVOXYL®. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and action of other drugs. A listing of drug-thyroidal axis interactions is contained in Table 2.

The list of drug-thyroidal axis interactions in Table 2 may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions. The 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 2: 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 (> 1 mcg/kg/min); Glucocorticoids (hydrocortisone ≥ 100 mg/day or equivalent); Octreotide (> 100 mcg/day).
Drugs that alter thyroid hormone secretion	
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodine (including iodine containing Radiographic contrast agents) Lithium Methimazole Propylthiouracil (PTU) 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 cholelystographic 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 Iodine (including iodine containing Radiographic contrast agents)	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Drugs that may decrease T₄ absorption, which may result in hypothyroidism	
Antacids – Aluminum & Magnesium Hydroxides – Simethicone Bile Acid Sequestrants – Cholestyramine – Colestipol Calcium Carbonate Cation Exchange Resins – Kayexalate Ferrous Sulfate Succralfate	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-tyrosine complex. Administer levothyroxine at least 4 hours apart from these agents.
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	
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heron / Methadone 5-Fluorouracil Mitotane Tamoxifen	Drugs that may decrease serum TBG concentration Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
Drugs that may cause protein-binding site displacement	
Furosemide (> 80 mg IV) Heparin Hydantoins Non-Steroidal Anti-Inflammatory Drugs – Penicillins – Phenytoin Saliicylates (> 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in FT ₄ . Continued administration results in a decrease in serum T ₄ and normal FT ₄ and TSH concentrations and, therefore, patients are clinically euthyroid. Saliicylates inhibit binding of T ₄ and T ₃ to TBG and thyroxin. An initial increase in serum FT ₄ is followed by return of FT ₄ to normal levels with sustained therapeutic serum saliicylate concentrations, although total-T ₄ levels may decrease by as much as 30%.

