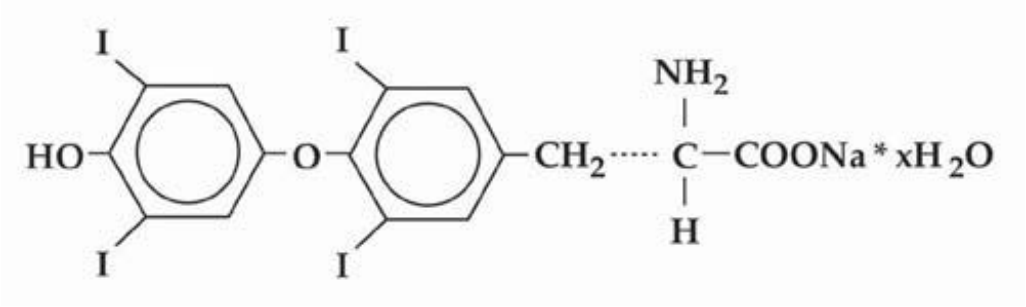
SYNTHROID - levothyroxine sodium tablet
REMEDYREPACK INC.

BOXED WARNING

WARNING: 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.

DESCRIPTION

SYNTHROID (levothyroxine sodium tablets, USP) contain synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T4) sodium]. Synthetic T4 is identical to that produced in the human thyroid gland. Levothyroxine (T4) sodium has an empirical formula of C15H10I4N NaO4H2O, molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



Inactive Ingredients

Acacia, confectioner's sugar (contains corn starch), lactose monohydrate, magnesium stearate, povidone, and talc. The following are the color additives by tablet strength:

Strength (mcg)Color additive(s)25FD&C Yellow No. 6 Aluminum Lake*50None75FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake88FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake*, D&C Yellow No. 10 Aluminum Lake100D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake*112D&C Red No. 27 & 30 Aluminum Lake125FD&C Yellow No. 6 Aluminum Lake*, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake137FD&C Blue No. 1 Aluminum Lake150FD&C Blue No. 2 Aluminum Lake175FD&C Blue No. 1 Aluminum Lake, D&C Red No. 27 & 30 Aluminum Lake200FD&C Red No. 40 Aluminum Lake300D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake*, FD&C Blue No. 1 Aluminum Lake*NoteFD&C Yellow No. 6 is orange in color.
Meets USP Dissolution Test 3

CLINICAL PHARMACOLOGY

Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of

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

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

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

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

Levothyroxine, 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 (seeINDICATIONS AND USAGE,PRECAUTIONS, andDOSAGE 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 SYNTHROID tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%. 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 (seePRECAUTIONS - Drug InteractionsandDrug-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 (seePRECAUTIONS - Drug InteractionsandDrug-Laboratory Test Interactions). Thyroid hormones do not readily cross the placental barrier (seePRECAUTIONS - Pregnancy).

Metabolism

T4 is slowly eliminated (seeTable 1). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T3 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
HormoneRatio in ThyroglobulinBiologic Potencyt1/2 (days)Protein Binding (%)2 Levothyroxine (T4)10 - 2016-7199.96Liothyronine (T3)14299.51 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism
2 Includes TBG, TBPA, and TBA

INDICATIONS & 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 (seeWARNINGSandPRECAUTIONS), including thyroid nodules (seeWARNINGSandPRECAUTIONS), subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter (seeWARNINGSandPRECAUTIONS) 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 (seePRECAUTIONS). SYNTHROID is contraindicated in patients with hypersensitivity to any of the inactive ingredients in SYNTHROID tablets (SeeDESCRIPTION - Inactive Ingredients).

WARNINGS
Boxed Warning
WARNING: 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.

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 (seeCONTRAINDICATIONS). 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.

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 (seeDrug Interactions).

Effects on Bone Mineral Density

In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than 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 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 (seeWARNINGS,PRECAUTIONS - Geriatric Use, andDOSAGE 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 (seeWARNINGS). If the serum TSH is already suppressed, levothyroxine sodium should not be administered (seeCONTRAINDICATIONS).

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 (seePRECAUTIONS - Autoimmune polyglandular syndromefor 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 (seePRECAUTIONS - 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 SYNTHROID:
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 SYNTHROID. 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 SYNTHROID 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 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 hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis).
5.Take SYNTHROID as a single dose, preferably on an empty stomach, one-half to one hour before breakfast. Levothyroxine absorption is increased on an empty stomach.
6.It may take several weeks before you notice an improvement in your symptoms.
7.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, heat intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.
8.Notify your physician if you become pregnant while taking SYNTHROID. It is likely that your dose of SYNTHROID will need to be increased while you are pregnant.
9.Notify your physician or dentist that you are taking SYNTHROID prior to any surgery.
10.Partial hair loss may occur rarely during the first few months of SYNTHROID therapy, but this is usually temporary.
11.SYNTHROID should not be used as a primary or adjunctive therapy in a weight control program.
12.Keep SYNTHROID out of the reach of children. Store SYNTHROID away from heat, moisture, and light.
13.Agents such as iron and calcium supplements and antacids can decrease the absorption of levothyroxine sodium tablets. Therefore, levothyroxine sodium tablets should not be administered

within 4 hours of these agents.

Laboratory Tests

General
The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay (second generation assay sensitivity0.1 mIU/L or third generation assay sensitivity0.01 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 (seePRECAUTIONS - Drug InteractionsandDrug-Laboratory Test Interactions). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of SYNTHROID 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 has 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 SYNTHROID (seeWARNINGS,PRECAUTIONS, andDOSAGE 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 SYNTHROID therapy and/or of the serum TSH to decrease below 20 mU/L within 4 weeks should alert the physician to the possibility that the child is not receiving adequate therapy. Careful inquiry should then be made regarding compliance, dose of medication administered, and method of administration prior to raising the dose of SYNTHROID.
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, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals(see PRECAUTIONS - Pediatric UseandDOSAGE AND ADMINISTRATION).

Secondary (Pituitary) and Tertiary (Hypothalamic) Hypothyroidism
Adequacy of therapy should be assessed by measuring serum free- T4 levels, which should be maintained in the upper half of the normal range in these patients.

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 inTable 2.
The list of drug-thyroidal axis interactions inTable 2may 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 ClassEffectDrugs that may reduce TSH secretion Dopamine/Dopamine Agonists
Glucocorticoids
OctreotideUse of these agents may result in a transient reduction in TSH secretion when administered at the following doses: Dopamine (**Drugs that alter thyroid hormone secretionDrugs that may decrease thyroid hormone secretion, which may result in hypothyroidism**Aminoglutethimide
Amiodarone
Iodide (including iodine-containing radiographic contrast agents)
Lithium
Methimazole
Propylthiouracil (PTU)
Sulfonamides
TolbutamideLong-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 T4 and T3 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 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
Orlistat
SucralfateConcurrent 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 4 hours apart from these agents. Patients treated concomitantly with orlistat and levothyroxine should be monitored for changes in thyroid function.**Drugs that may increase serum TBG concentrationDrugs that may decrease serum TBG concentration**Clofibrate
Estrogen-containing oral contraceptives
Estrogens (oral)
Heroin / Methadone
5-Fluorouracil
Mitotane
TamoxifenAndrogens / 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
- Fenamates
- Phenylbutazone
Salicylates (> 2 g/day)Administration of these agents with levothyroxine results in an initial transient increase in FT4. Continued administration results in a decrease in serum T4 and normal FT4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T4 and T3 to TBG and transthyretin. An initial increase in serum FT4 is followed by return of FT4 to normal levels with sustained therapeutic serum salicylate concentrations, although total-T4 levels may decrease by as much as 30%.**Drugs that may alter T4 and T3 metabolismDrugs that may increase hepatic metabolism, which may result in hypothyroidism**Carbamazepine
Hydantoins
Phenobarbital
RifampinStimulation 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- T4 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 > 160 mg/day)
Glucocorticoids
- (e.g., Dexamethasone4 mg/day)
Propylthiouracil (PTU)Administration of these enzyme inhibitors decreases the peripheral conversion of T4 to T3, leading to decreased T3 levels. However, serum T4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (> 160 mg/day), T3 and T4 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 T3 concentrations by 30% with minimal change in serum T4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T3 and T4 levels due to decreased TBG production (see above).**Miscellaneous**Anticoagulants (oral)
- Coumarin Derivatives
- Indandione DerivativesThyroid 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 InhibitorsAntidiabetic Agents
- Biguanides
- Meglitinides
- Sulfonylureas
- Thiazolidinediones
- InsulinAddition 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.Cardiac GlycosidesSerum 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-
- Interleukin-2Therapy with interferon-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-and -have not been reported to cause thyroid dysfunction.Growth Hormones
- Somatrem
- SomatropinExcessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.KetamineMethylxanthine Bronchodilators
- (e.g., Theophylline)Radiographic AgentsThyroid hormones may reduce the uptake of 123I, 131I, and 99mTc.SympathomimeticsConcurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.Chloral Hydrate
Diazepam
Ethionamide
Lovastatin
Metoclopramide
6-Mercaptopurine
Nitroprusside
Para-aminosalicylate sodium
Perphenazine
Resorcinol (excessive topical use)
Thiazide DiureticsThese agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.
Oral anticoagulants
Levothyroxine increases 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 SYNTHROID dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (seeTable 2).

Digitalis glycosides
The therapeutic effects of digitalis glycosides may be reduced by levothyroxine. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (seeTable 2).

Drug-Food Interactions
Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the GI tract.

Drug-Laboratory Test Interactions

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

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

Pregnancy

Category A
Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Therefore, the possibility of fetal harm appears remote. SYNTHROID should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.
Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. During pregnancy, serum T4 levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women taking SYNTHROID should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of SYNTHROID. Since postpartum TSH levels are similar to preconception values, the SYNTHROID dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-8 weeks postpartum.
Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent in utero hypothyroidism.

Nursing Mothers
Although thyroid hormones are excreted only minimally in human milk, caution should be exercised when SYNTHROID is administered to a nursing woman. However, adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

Pediatric Use

General
The goal of treatment in pediatric patients with hypothyroidism is to achieve and maintain normal intellectual and physical growth and development.
The initial dose of levothyroxine varies with age and body weight (see DOSAGE AND ADMINISTRATION - Table 3). Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters (see PRECAUTIONS - Laboratory Tests).
In children in whom a diagnosis of permanent hypothyroidism has not been established, it is recommended that levothyroxine administration be discontinued for a 30-day trial period, but only after the child is at least 3 years of age. Serum T4 and TSH levels should then be obtained. If the T4 is low and the TSH high, the diagnosis of permanent hypothyroidism is established, and levothyroxine therapy

should be reinstituted. If the T4 and TSH levels are normal, euthyroidism may be assumed and, therefore, the hypothyroidism can be considered to have been transient. In this instance, however, the physician should carefully monitor the child and repeat the thyroid function tests if any signs or symptoms of hypothyroidism develop. In this setting, the clinician should have a high index of suspicion of relapse. If the results of the levothyroxine withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.
Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, an alternate approach is to reduce the replacement dose of levothyroxine by half during the 30-day trial period. If, after 30 days, the serum TSH is elevated above 20 mU/L, the diagnosis of permanent hypothyroidism is confirmed, and full replacement therapy should be resumed. However, if the serum TSH has not risen to greater than 20 mU/L, levothyroxine treatment should be discontinued for another 30-day trial period followed by repeat serum T4 and TSH testing.
The presence of concomitant medical conditions should be considered in certain clinical circumstances and, if present, appropriately treated (seePRECAUTIONS).

Congenital Hypothyroidism
(seePRECAUTIONS - Laboratory TestsandDOSAGE AND ADMINISTRATION)
Rapid restoration of normal serum T4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, SYNTHROID therapy should be initiated immediately upon diagnosis and is generally continued for life.
During the first 2 weeks of SYNTHROID therapy, infants should be closely monitored for cardiac overload, arrhythmias, and aspiration from avid suckling.
The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

Acquired Hypothyroidism in Pediatric Patients
The patient should be monitored closely to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.
Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

Geriatric Use
Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (seeWARNINGS,PRECAUTIONS, andDOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage (seePRECAUTIONSandOVERDOSAGE). They include the following:

General
fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating;

Central nervous system
headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia;

Musculoskeletal
tremors, muscle weakness;

Cardiovascular
palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest;

Respiratory
dyspnea;

Gastrointestinal
diarrhea, vomiting, abdominal cramps and elevations in liver function tests;

Dermatologic
hair lss, flushing;

Endocrine
decreased bone mineral density;

Reproductive
menstrual irregularities, impaired fertility.

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.
Seizures have been reported rarely with the institution of levothyroxine therapy.
Inadequate levothyroxine dosage will produce or fail to ameliorate the signs and symptoms of hypothyroidism.
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.

Overdosage
The signs and symptoms of overdosage are those of hyperthyroidism (seePRECAUTIONSandADVERSE REACTIONS). 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. Symptoms may not necessarily be evident or may not appear until several days after ingestion of levothyroxine sodium.

Treatment of Overdosage
Levothyroxine sodium should be reduced in dose or temporarily discontinued if signs or symptoms of overdosage occur.

Acute Massive Overdosage
This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. If not contraindicated (e.g., by seizures, coma, or loss of the gag reflex), the stomach should be emptied by emesis or gastric lavage to decrease gastrointestinal absorption. Activated charcoal or cholestyramine may also be used to decrease absorption. Central and peripheral increased sympathetic activity may be treated by administering B-receptor antagonists, e.g., propranolol, provided there are no medical contraindications to their use. Provide respiratory support as needed; control congestive heart failure and arrhythmia; control fever, hypoglycemia, and fluid loss as

necessary. Large doses of antithyroid drugs (e.g., methimazole or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthestis and release of thyroid hormones. Glucocorticoids may be given to inhibit the conversion of T4 to T3. Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Because T4 is highly protein bound, very little drug will be removed by dialysis.

DOSAGE & ADMINISTRATION

General Principles

The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state. The goal of suppressive therapy is to inhibit growth and/or function of abnormal thyroid tissue. The dose of SYNTHROID that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (seeWARNINGSandPRECAUTIONS). Hence, the following recommendations serve only as dosing guidelines. Dosing must be individualized and adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters (seePRECAUTIONS - Laboratory Tests).
SYNTHROID is administered as a single daily dose, preferably one-half to one-hour before breakfast. SYNTHROID should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (seePRECAUTIONS - Drug Interactions).
Due to the long half-life of levothyroxine, the peak therapeutic effect at a given dose of levothyroxine sodium may not be attained for 4-6 weeks.
Caution should be exercised when administering SYNTHROID to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (seePRECAUTIONS).

Specific Patient Populations

Hypothyroidism in Adults and in Children in Whom Growth and Puberty are Complete (seeWARNINGSandPRECAUTIONS - Laboratory Tests)
Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have been recently treated for hyperthyroidism or who have been hypothyroid for only a short time (such as a few months). The average full replacement dose of levothyroxine sodium is approximately 1.7 mcg/kg/day (e.g.,**100-125 mcg/dayfor a 70 kg adult). Older patients may require less than 1 mcg/kg/day. Levothyroxine sodium doses greater than 200 mcg/day are seldom required. An inadequate response to daily doses300 mcg/day is rare and may indicate poor compliance, malabsorption, and/or drug interactions.**
For most patients older than 50 years or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of 2**5-50 mcg/dayof levothyroxine sodium is recommended, with gradual increments in dose at 6-8 week intervals, as needed. The recommended starting dose of levothyroxine sodium in elderly patients with cardiac disease is 12.5-25 mcg/day , with gradual dose increments at 4-6 week intervals. The levothyroxine sodium dose is generally adjusted in12.5-25 mcgincrements until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized.**
In patients with severe hypothyroidism, the recommended initial levothyroxine sodium dose is 1**2.5-25 mcg/day with increases of 25 mcg/day every 2-4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized.**
In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the levothyroxine sodium dose should be titrated until the patient is clinically euthyroid and the serum free- T4 level is restored to the upper half of the normal range.

Pediatric Dosage - Congenital or Acquired Hypothyroidism

(seePRECAUTIONS - Laboratory Tests)

General Principles
In general, levothyroxine therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development.
Undertreatment and overtreatment should be avoided (seePRECAUTIONS - Pediatric Use).
SYNTHROID may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5-10 mL or 1-2 teaspoons) of water. This suspension can be administered by spoon or by dropper.**DO NOT STORE THE SUSPENSION.Foods that decrease absorption of levothyroxine, such as soybean infant formula, should not be used for administering levothyroxine sodium tablets (seePRECAUTIONS - Drug-Food Interactions).**

Newborns
The recommended starting dose of levothyroxine sodium in newborn infants is**10-15 mcg/kg/day. A lower starting dose (e.g.,25 mcg/day) should be considered in infants at risk for cardiac failure, and the dose should be increased in 4-6 weeks as needed based on clinical and laboratory response to treatment. In infants with very low (< 5 mcg/dL) or undetectable serum T4 concentrations, the recommended initial starting dose is50 mcg/dayof levothyroxine sodium.**

Infants and Children
Levothyroxine therapy is usually initiated at full replacement doses, with the recommended dose per body weight decreasing with age (seeTable 3). However, in children with chronic or severe hypothyroidism, an initial dose of**25 mcg/dayof levothyroxine sodium is recommended with increments of 25 mcg every 2-4 weeks until the desired effect is achieved.**
Hyperactivity in an older child can be minimized if the starting dose is one-fourth of the recommended full replacement dose, and the dose is then increased on a weekly basis by an amount equal to one-fourth the full-recommended replacement dose until the full recommended replacement dose is reached.

Table 3. Levothyroxine Sodium Dosing Guidelines for Pediatric Hypothyroidism
AGEDaily Dose Per Kg Body Weighta0-3 months10-15 mcg/kg/day3-6 months8-10 mcg/kg/day6-12 months6-8 mcg/kg/day1-5 years5-6 mcg/kg/day6-12 years4-5 mcg/kg/day> 12 years but growth and puberty incomplete2-3 mcg/kg/dayGrowth and puberty complete1.7 mcg/kg/daya The dose should be adjusted based on clinical response and laboratory parameters (seePRECAUTIONS - Laboratory TestsandPediatric Use).
Pregnancy
Pregnancy may increase levothyroxine requirements (seePREGNANCY).

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

TSH Suppression in Well-differentiated Thyroid Cancer and Thyroid Nodules
The target level for TSH suppression in these conditions has not been established with controlled studies. In addition, the efficacy of TSH suppression for benign nodular disease is controversial. Therefore, the dose of SYNTHROID used for TSH suppression should be individualized based on the specific disease and the patient being treated.
In the treatment of well-differentiated (papillary and follicular) thyroid cancer, levothyroxine is used as an adjunct to surgery and radioiodine therapy. Generally, TSH is suppressed to < 0.1 mU/L, and this

usually requires a levothyroxine sodium dose of**greater than 2 mcg/kg/day.However, in patients with high-risk tumors, the target level for TSH suppression may be < 0.01 mU/L.**
In the treatment of benign nodules and nontoxic multinodular goiter, TSH is generally suppressed to a higher target (e.g., 0.1 to either 0.5 or 1.0 mU/L) than that used for the treatment of thyroid cancer. Levothyroxine sodium is contraindicated if the serum TSH is already suppressed due to the risk of precipitating overt thyrotoxicosis (seeCONTRAINDICATIONS,WARNINGSandPRECAUTIONS).

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

HOW SUPPLIED

SYNTHROID (levothyroxine sodium tablets, USP)are round, color coded, scored and debossed with "SYNTHROID" on one side and potency on the other side. They are supplied as follows:

Strength (mcg)ColorNDC# for bottles of
90**NDC # for bottles of 100NDC # for bottles of 1000NDC # for unit dose cartons of 100**25orange0074-4341-900074-4341-130074-4341-19--50white0074-4552-900074-4552-130074-4552-190074-4552-1175violet0074-5182-900074-5182-130074-5182-190074-5182-1188olive0074-6594-900074-6594-130074-6594-19--100yellow0074-6624-900074-6624-130074-6624-190074-6624-11112rose0074-9296-900074-9296-130074-9296-19--125brown0074-7068-900074-7068-130074-7068-190074-7068-11137turquoise0074-3727-900074-3727-130074-3727-19--150blue0074-7069-900074-7069-130074-7069-190074-7069-11175lilac0074-7070-900074-7070-130074-7070-19--200pink0074-7148-900074-7148-130074-7148-190074-7148-11300green0074-7149-900074-7149-130074-7149-19--

STORAGE AND HANDLING

Store at 25 C (77 F); excursions permitted to 15-30 C (59-86 F)[see USP Controlled Room Temperature]. SYNTHROID tablets should be protected from light and moisture

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION

DRUG: Synthroid
GENERIC: LEVOTHYROXINE SODIUM
DOSAGE: TABLET
ADMINSTRATION: ORAL
NDC: 52125-116-02
STRENGTH:200 ug
COLOR: pink
SHAPE: ROUND
SCORE: Two even pieces
SIZE: 7 mm
IMPRINT: 30
QTY: 30

SYNTHROID TABLET

200 MCG (0.2 MG) QTY:00030

NDC#:52125-0116-02 INT:MS ID#:200

EXPIRES: 07/2013

LOT#: DP712012345

COL: pink SHP:round

DIST: ABBOTT LABS NORTH CHICAGO IL 60064

MFG: ABBOTT LABS NORTH CHICAGO IL 60064

A. Caution Federal law prohibits transfer of this drug to any person other than for whom it was prescribed.

B. Store at a temperature between 15 degree C and 30 degree C (59 degree F and 86 degree F) {see USP}

C. Re-packaged by: RemedyRepack Inc. 655 Kolter Dr., Indiana, PA 15701, 1-724-465-8762

SYNTHROID

levothyroxine sodium tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:52125-116(NDC:0074-7148)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVOTHYROXINE SODIUM (LEVOTHYROXINE)	LEVOTHYROXINE SODIUM ANHYDROUS	200 ug

Inactive Ingredients

Ingredient Name	Strength
ACACIA	
LACTOSE MONOHYDRATE	

MAGNESIUM STEARATE	
POVIDONE	
TALC	
FD&C RED NO. 40	

Product Characteristics

Color	pink	**Score**	2 pieces
Shape	ROUND (TABLET)	**Size**	7mm
Flavor		**Imprint Code**	SYNTHROID;200
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52125-116-02	30 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021402	09/27/2012	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 9/2012 REMEDYREPACK INC.