

LEVOTHYROXINE SODIUM- levothyroxine sodium tablet
Northwind Pharmaceuticals, LLC

LEVOTHYROXINE SODIUM

BOXED WARNING

WARNING:

Thyroid hormones, including Levothyroxine sodium tablets, USP, 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

Levothyroxine sodium tablets, USP contains synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T4) sodium]. Synthetic T4 is identical to that produced in the human thyroid gland.

Levothyroxine (T4) sodium has an empirical formula of $C_{15}H_{10}I_4N NaO_4 \times H_2O$, molecular weight of 798.86 g/mol (anhydrous).

Inactive Ingredients

Magnesium Stearate, NF; Microcrystalline Cellulose, NF; Colloidal Silicone Dioxide, NF; Sodium Starch Glycolate, NF, FD&C Blue No. 1 Aluminum Lake.

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 (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 this brand of Levothyroxine sodium tablets, USP product, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%. T4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T4. Absorption may also decrease with age. In addition, many drugs and foods affect T4 absorption (see 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 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.

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 (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). Levothyroxine sodium tablets, USP is contraindicated in patients with hypersensitivity to any of the inactive ingredients in Levothyroxine sodium tablets, USP, (see DESCRIPTION, Inactive Ingredients.)

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 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 (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 Levothyroxine sodium tablets, USP:

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.

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 Levothyroxine sodium tablets, USP. 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.

Use Levothyroxine sodium tablets, USP 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.

The levothyroxine in Levothyroxine sodium tablets, USP 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).

Take Levothyroxine sodium tablets, USP as a single dose, preferably on an empty stomach, one-half to one hour before breakfast. Levothyroxine absorption is increased on an empty stomach.

Levothyroxine sodium tablets, USP may rapidly disintegrate. It is very important that you take the tablet with a full glass of water.

It may take several weeks before you notice an improvement in your symptoms.

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.

Notify your physician if you become pregnant while taking Levothyroxine sodium tablets, USP. It is likely that your dose of Levothyroxine sodium tablets, USP will need to be increased while you are pregnant.

Notify your physician or dentist that you are taking Levothyroxine sodium tablets, USP prior to any surgery.

Partial hair loss may occur rarely during the first few months of Levothyroxine sodium tablets, USP therapy, but this is usually temporary.

Levothyroxine sodium tablets, USP should not be used as a primary or adjunctive therapy in a weight

control program.

Keep Levothyroxine sodium tablets, USP out of the reach of children. Store Levothyroxine sodium tablets, USP away from heat, moisture, and light.

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 hrs of these agents.

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 Levothyroxine sodium tablets, USP 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 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 Levothyroxine sodium tablets, USP (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 Levothyroxine sodium tablets, USP 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 Levothyroxine sodium tablets, USP.

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 Levothyroxine sodium tablets, USP 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

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. 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 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 (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 Levothyroxine sodium tablets, USP:

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.

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 Levothyroxine sodium tablets, USP. 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.

Use Levothyroxine sodium tablets, USP 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.

The levothyroxine in Levothyroxine sodium tablets, USP 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).

Take Levothyroxine sodium tablets, USP as a single dose, preferably on an empty stomach, one-half to one hour before breakfast. Levothyroxine absorption is increased on an empty stomach.

Levothyroxine sodium tablets, USP may rapidly disintegrate. It is very important that you take the tablet with a full glass of water.

It may take several weeks before you notice an improvement in your symptoms.

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.

Notify your physician if you become pregnant while taking Levothyroxine sodium tablets, USP. It is likely that your dose of Levothyroxine sodium tablets, USP will need to be increased while you are pregnant.

Notify your physician or dentist that you are taking Levothyroxine sodium tablets, USP prior to any surgery.

Partial hair loss may occur rarely during the first few months of Levothyroxine sodium tablets, USP therapy, but this is usually temporary.

Levothyroxine sodium tablets, USP should not be used as a primary or adjunctive therapy in a weight control program.

Keep Levothyroxine sodium tablets, USP out of the reach of children. Store Levothyroxine sodium tablets, USP away from heat, moisture, and light.

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 hrs of these agents.

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 Levothyroxine sodium tablets, USP 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 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 Levothyroxine sodium tablets, USP (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 Levothyroxine sodium tablets, USP 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 Levothyroxine sodium tablets, USP.

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 Levothyroxine sodium tablets, USP 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

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 Levothyroxine sodium tablets, USP. 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 at the manufacturer's site here:**
<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a3845f91-e0fe-42aa-8043-aeaac43f8eef>

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 Levothyroxine sodium tablets, USP dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see Link).

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 (see Table 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 Levothyroxine sodium tablets, USP 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 Levothyroxine sodium tablets, USP 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. Levothyroxine sodium tablets, USP 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 Levothyroxine sodium tablets, USP should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of Levothyroxine sodium tablets, USP. Since postpartum TSH levels are similar to preconception values, the Levothyroxine sodium tablets, USP 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 Levothyroxine sodium tablets, USP are 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 reinstated. 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 (see PRECAUTIONS).

Congenital Hypothyroidism (see PRECAUTIONS, Laboratory Tests and DOSAGE 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, Levothyroxine sodium tablets, USP therapy should be initiated immediately upon diagnosis and is generally continued for life.

During the first 2 weeks of Levothyroxine sodium tablets, USP 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 (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage (see PRECAUTIONS and OVERDOSAGE). 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 loss, flushing;

Endocrine: decreased bone mineral density;

Reproductive: menstrual irregularities, impaired fertility.

Pseudotumor cerebri and slipped capital femoral epiphyses 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 (see PRECAUTIONS and ADVERSE 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 β -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 synthesis and release of thyroid hormones. Glucocorticoids may be given to inhibit the conversion of T4 to T3. Plasmapheresis, charcoal hemoperfusion, and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Because T4 is highly protein bound, very little drug will be removed by dialysis.

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 Levothyroxine sodium tablets, USP that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see WARNINGS and PRECAUTIONS). 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 (see PRECAUTIONS, Laboratory Tests).

Levothyroxine sodium tablets, USP are administered as a single daily dose, preferably one-half to one-hour before breakfast. Levothyroxine sodium tablets, USP should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (see PRECAUTIONS, Drug Interactions). Levothyroxine sodium tablets, USP should be taken with a full glass of water, (see Information for Patients).

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

Caution should be exercised when administering Levothyroxine sodium tablets, USP to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (see PRECAUTIONS).

Specific Patient Populations

Hypothyroidism in Adults and in Children in Whom Growth and Puberty are Complete (see WARNINGS and PRECAUTIONS, Laboratory Tests)

Therapy may begin at full replacement doses in otherwise healthy individuals who are at low risk of coronary artery disease. The average full replacement dose of levothyroxine sodium is approximately 1.7 mcg/kg/day (e.g., 100-125 mcg/day for a 70 kg adult). Older patients may require less than 1 mcg/kg/day. Levothyroxine sodium doses greater than 200 mcg/day are seldom required. An inadequate response to daily doses \geq 300 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 25-50 mcg/day of 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 in 12.5-25 mcg increments 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 12.5-25 mcg/day with increases of 25 mcg/day every 2-4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized.

In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the levothyroxine sodium dose should be titrated until the patient is clinically euthyroid and the serum free-T4 level is

restored to the upper half of the normal range.

Pediatric Dosage – Congenital or Acquired Hypothyroidism (see PRECAUTIONS, 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 (see PRECAUTIONS, Pediatric Use).

Levothyroxine sodium tablets, USP may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5-10 mL or 1-2 teaspoons) of water. This suspension can be administered by spoon or dropper. **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 (see PRECAUTIONS , 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 is 50 mcg/day of levothyroxine sodium.

Infants and Children

Levothyroxine therapy is usually initiated at full replacement doses, with the recommended dose per body weight decreasing with age (see Table 3). However, in children with chronic or severe hypothyroidism, an initial dose of 25 mcg/day of 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 CAN BE FOUND HERE: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a3845f91-e0fe-42aa-8043-aeaac43f8eef>

Pregnancy- Pregnancy may increase levothyroxine requirements (see Pregnancy).

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 Levothyroxine sodium tablets, USP 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 (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

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. Intravenous levothyroxine sodium should be administered.

PRINCIPAL DISPLAY PANEL

NDC: 51655-299-52

MFG: 0781-5191-92

Levothyroxine Sodium 137 MCG

30 Tablets

Rx Only

Lot#

Exp. Date:

Each tablet contains: levothyroxine sodium...137mcg

Dosage: See prescriber's instructions

Store in this light-resistant container.

Keep out of the reach of children

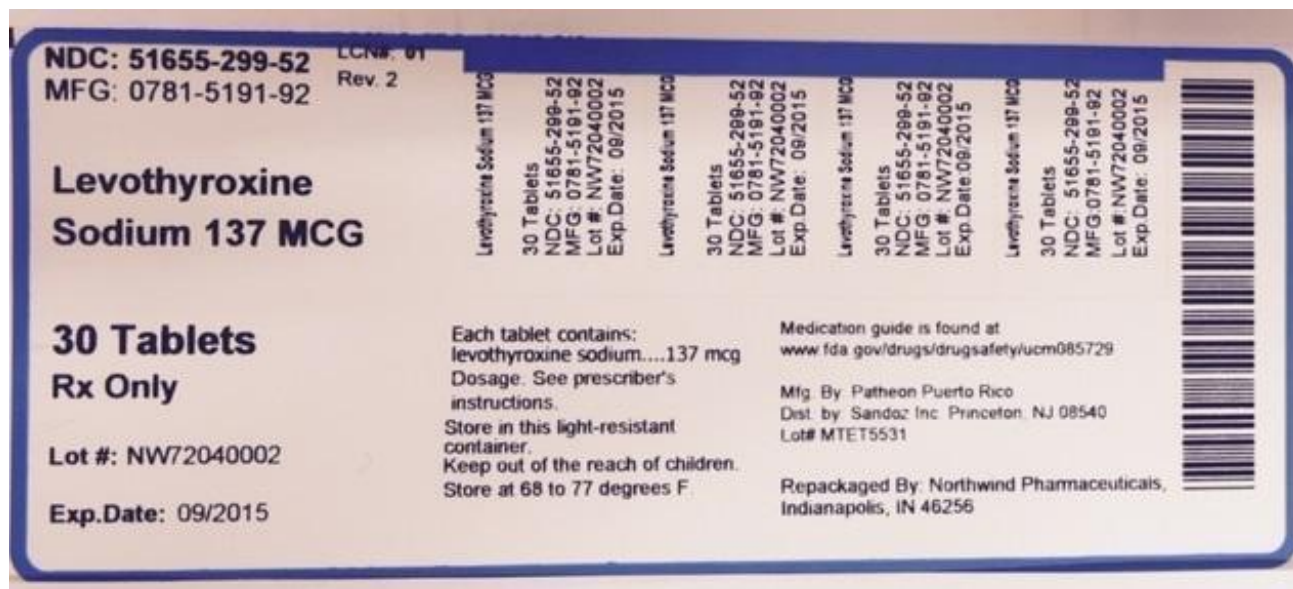
Store at 68 to 77 degrees F.

Medication guide is found at www.fda.gov/drugs/drugsafety/ucm085729

Mfg. by Patheon Puerto Rico

Dist. by Sandoz Inc. Princeton, NJ 08540 Lot#

Repackaged by Northwind Pharmaceuticals, Indianapolis, IN 46256



LEVOTHYROXINE SODIUM

levothyroxine sodium tablet

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|------------------------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51655-299(NDC:0781-5191) |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|--------------------------------|-----------------|
| LEVOTHYROXINE SODIUM (UNII: 9J765S329G) (LEVOTHYROXINE - UNII:Q51BO43MG4) | LEVOTHYROXINE SODIUM ANHYDROUS | 0.137 mg |

Product Characteristics

| | | | |
|-----------------|-------|---------------------|------------|
| Color | green | Score | 2 pieces |
| Shape | OVAL | Size | 9mm |
| Flavor | | Imprint Code | 137;GG;330 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|----------------------------|-----------------------------|---------------------------|
| 1 | NDC:51655-299-52 | 30 in 1 BOTTLE, DISPENSING | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---------------------------|---|-----------------------------|---------------------------|
| NDA | NDA021342 | 02/04/2015 | |

Labeler - Northwind Pharmaceuticals, LLC (036986393)**Registrant** - Northwind Pharmaceuticals, LLC (036986393)**Establishment**

| Name | Address | ID/FEI | Business Operations |
|--------------------------------|----------------|---------------|----------------------------|
| Northwind Pharmaceuticals, LLC | | 036986393 | repack(51655-299) |

Revised: 3/2015

Northwind Pharmaceuticals, LLC