This information is intended for U.S. residents only.

# SYNTHROID®

**(levothyroxine sodium, USP)**

**SYNTHROID Tablets** – for oral administration

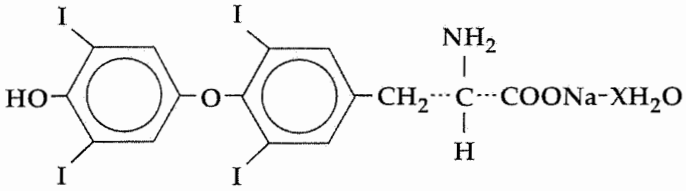
**SYNTHROID Injection** – for parenteral administration

**℞ only**



**DESCRIPTION:** SYNTHROID (levothyroxine sodium, USP) Tablets and Injection contain synthetic crystalline L-3, 3', 5, 5'-tetraiodothyronine sodium salt [levothyroxine ($T_4$) sodium]. Synthetic $T_4$ is identical to that produced in the human thyroid gland.

Levothyroxine ($T_4$) Sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4xH_2O$, molecular weight of 798.86 (anhydrous), and structural formula as shown:




LEVOTHYROXINE SODIUM

**Inactive Ingredients (SYNTHROID Tablets):** acacia, confectioner's sugar (contains corn starch), lactose, magnesium stearate, povidone, talc. The following are the color additives by tablet strength:

| Strength (mcg) | Color Additive(s) |
|---|---|
| 25 | FD&C Yellow No. 6 |
| 50 | None |
| 75 | FD&C Red No. 40, FD&C Blue No. 2 |
| 88 | FD&C Blue No. 1, FD&C Yellow No. 6, D&C Yellow No. 10 |
| 100 | D&C Yellow No. 10, FD&C Yellow No. 6 |
| 112 | D&C Red No. 27 & 30 |
| 125 | FD&C Yellow No. 6, FD&C Red No. 40, FD&C Blue No. 1 |
| 150 | FD&C Blue No. 2 |
| 175 | FD&C Blue No. 1, D&C Red No. 27 & 30 |
| 200 | FD&C Red No. 40 |
| 300 | D&C Yellow No. 10, FD&C Yellow No. 6, FD&C Blue No. 1 |

**Inactive Ingredients (SYNTHROID Injection):** 10 mg mannitol, USP, 0.7 mg tribasic sodium phosphate, anhydrous (200 mcg/vial), 1.75 mg tribasic sodium phosphate, anhydrous (500 mcg/vial), sodium hydroxide, Q.S. for pH adjustment.

Levothyroxine sodium powder for reconstitution for injection is a sterile preparation.

**CLINICAL PHARMACOLOGY:** The synthesis and secretion of the major thyroid hormones, L-thyroxine ($T_4$) and L-triiodothyronine ($T_3$), from the normally functioning thyroid gland are regulated by complex feedback mechanisms of the hypothalamic-pituitary-thyroid axis. The thyroid gland is stimulated to secrete thyroid hormones by the action of thyrotropin (thyroid stimulating hormone, TSH), which is produced in the anterior pituitary gland. TSH secretion is in turn controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus, circulating thyroid hormones, and possibly other mechanisms. Thyroid hormones circulating in the blood act as feedback inhibitors of both TSH and TRH secretion. Thus, when serum concentrations of $T_3$ and $T_4$ are increased, secretion of TSH and TRH decreases. Conversely, when serum thyroid hormone concentrations are decreased, secretion of TSH and TRH is increased. Administration of exogenous thyroid hormones to euthyroid individuals results in suppression of endogenous thyroid hormone secretion.

The mechanisms by which thyroid hormones exert their physiologic actions have not been completely elucidated. $T_4$ and $T_3$ are transported into cells by passive and active mechanisms. $T_3$ in cell cytoplasm and $T_3$ generated from $T_4$ within the cell diffuse into the nucleus and bind to thyroid receptor proteins, which appear to be primarily attached to DNA. Receptor binding leads to activation or repression of DNA transcription, thereby altering the amounts of mRNA and resultant proteins. Changes in protein concentrations are responsible for the metabolic changes observed in organs and tissues.

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

The physiologic effects of thyroid hormones are produced primarily by $T_3$, a large portion of which is derived from the deiodination of $T_4$ in peripheral tissues. About 70 to 90 percent of peripheral $T_3$ is produced by monodeiodination of $T_4$ at the 5' position (outer ring). Peripheral monodeiodination of $T_4$ at the 5 position (inner ring) results in the formation of reverse triiodothyronine ($rT_3$), which is calorigenically inactive.

**PHARMACOKINETICS:** Few clinical studies have evaluated the kinetics of orally administered thyroid hormone. In animals, the most active sites of absorption appear to be the proximal and mid-jejunum. $T_4$ is not absorbed from the stomach and little, if any, drug is absorbed from the duodenum. There seems to be no absorption of $T_4$ from the distal colon in animals. A number of human studies have confirmed the importance of an intact jejunum and ileum for $T_4$ absorption and have shown some absorption from the duodenum. Studies involving radioiodinated $T_4$ fecal tracer excretion methods, equilibration, and AUC methods have shown that absorption varies from 48 to 80 percent of the administered dose. The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes, such as sprue. Absorption may also decrease with age. The degree of $T_4$ absorption is dependent on the product formulation as well as on the character of the intestinal contents, including plasma protein and soluble dietary factors, which bind thyroid hormone making it unavailable for diffusion. Decreased absorption may result from administration of infant soybean formula, ferrous sulfate, sodium polystyrene sulfonate, aluminum hydroxide, sucralfate, or bile acid sequestrants. $T_4$ absorption following intramuscular administration is variable.

Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated. More than 99 percent of circulating hormones is bound to serum proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA). $T_4$ is more extensively and firmly bound to serum proteins than is $T_3$. Only unbound thyroid hormone is metabolically active. The higher affinity of TBG and TBPA for $T_4$ partly explains the higher serum levels, slower metabolic clearance, and longer serum elimination half-life of this hormone.

Certain drugs and physiologic conditions can alter the binding of thyroid hormones to serum proteins and/or the concentrations of the serum proteins available for thyroid hormone binding. These effects must be considered when interpreting the results of thyroid function tests. (See **Drug Interactions** and **Laboratory Test Interactions**.)

$T_4$ is eliminated slowly from the body, with a half-life of 6 to 7 days. $T_3$ has a half-life of 1 to 2 days. The liver is the major site of degradation for both hormones. $T_4$ and $T_3$ are conjugated with glucuronic and sulfuric acids and excreted in the bile. There is an enterohepatic circulation of thyroid hormones, as they are liberated by hydrolysis in the intestine and reabsorbed. A portion of the conjugated material reaches the colon unchanged, is hydrolyzed there, and is eliminated as free compounds in the feces. In man, approximately 20 to 40 percent of $T_4$ is eliminated in the stool. About 70 percent of the $T_4$ secreted daily is deiodinated to yield equal amounts of $T_3$ and $rT_3$. Subsequent deiodination of $T_3$ and $rT_3$ yields multiple forms of diiodothyronine. A number of other minor $T_4$ metabolites have also been identified. Although some of these metabolites have biologic activity, their overall contribution to the therapeutic effect of $T_4$ is minimal.

**INDICATIONS AND USAGE:** SYNTHROID is indicated:

1. As replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis: primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of the thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism (see **CONTRAINDICATIONS** and **PRECAUTIONS**). SYNTHROID **Injection** can be used intravenously when rapid repletion is required, and either intravenously or intramuscularly when the oral route is precluded.

2. As a pituitary TSH suppressant in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter, and in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

**CONTRAINDICATIONS:** SYNTHROID is contraindicated in patients with untreated thyrotoxicosis of any etiology or an apparent hypersensitivity to thyroid hormones or any of the inactive product constituents. (The 50 mcg tablet is formulated without color additives for patients who are sensitive to dyes.) There is no well-documented evidence of true allergic or idiosyncratic reactions to thyroid hormone. SYNTHROID is also contraindicated in the patients with uncorrected adrenal insufficiency, as thyroid hormones increase tissue demands for adrenocortical hormones and may thereby precipitate acute adrenal crisis (see **PRECAUTIONS**).

**WARNINGS:** Thyroid hormones, either alone or together with other therapeutic agents, should not be used for the treatment of obesity. 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.

The use of SYNTHROID in the treatment of obesity, either alone or in combination with other drugs, is unjustified. The use of SYNTHROID is also unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

**PRECAUTIONS: General:** SYNTHROID should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, and hypertension, and in the elderly who have a greater likelihood of occult cardiac disease. Concomitant administration of thyroid hormone and sympathomimetic agents to patients with coronary artery disease may increase the risk of coronary insufficiency.

Use of SYNTHROID in patients with concomitant diabetes mellitus, diabetes insipidus or adrenal cortical insufficiency may aggravate the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases may therefore be required. Treatment of myxedema coma may require simultaneous administration of glucocorticoids (see **DOSAGE AND ADMINISTRATION**).

$T_4$ enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both SYNTHROID and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly.

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

Lithium blocks the TSH-mediated release of $T_4$ and $T_3$. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual SYNTHROID dose may be required.

**Information for the Patient:**

1. SYNTHROID is intended to replace a hormone that is normally produced by your thyroid gland. It is generally taken for life, except in cases of temporary hypothyroidism associated with an inflammation of the thyroid gland.

2. Before or at any time while using SYNTHROID you should tell your doctor if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding, are taking or start taking any other prescription or nonprescription (OTC) medications, or have any other medical problems (especially hardening of the arteries, heart disease, high blood pressure, or history of thyroid, adrenal or pituitary gland problems).

3. Use SYNTHROID only as prescribed by your doctor. Do not discontinue SYNTHROID or change the amount you take or how often you take it, except as directed by your doctor.

4. SYNTHROID, like all medicines obtained from your doctor, must be used only by you and for the condition determined appropriate by your doctor.

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

6. You should notify your doctor if you experience any of the following symptoms, or if you experience any other unusual medical event: chest pain, shortness of breath, hives or skin rash, rapid or irregular heartbeat, headache, irritability, nervousness, sleeplessness, diarrhea, excessive sweating, heat intolerance, changes in appetite, vomiting, weight gain or loss, changes in menstrual periods, fever, hand tremors, leg cramps.

7. You should inform your doctor or dentist that you are taking SYNTHROID before having any kind of surgery.

8. You should notify your doctor if you become pregnant while taking SYNTHROID. Your dose of this medicine will likely have to be increased while you are pregnant.

9. If you have diabetes, your dose of insulin or oral antidiabetic agent may need to be changed after starting SYNTHROID. You should monitor your blood or urinary glucose levels as directed by your doctor and report any changes to your doctor immediately.

10. If you are taking an oral anticoagulant drug such as warfarin, your dose may need to be changed after starting SYNTHROID. Your coagulation status should be checked often to determine if a change in dose is required.

11. Partial hair loss may occur rarely during the first few months of SYNTHROID therapy, but it is usually temporary.

12. SYNTHROID is the trade name for tablets containing the thyroid hormone levothyroxine, manufactured by Abbott Laboratories. Other manufacturers also make tablets containing levothyroxine. You should not change to another manufacturer's product without discussing that change with your doctor first. Repeat blood tests and a change in the amount of levothyroxine you take may be required.

13. Keep SYNTHROID out of the reach of children. Store SYNTHROID away from heat and moisture.

**Laboratory Tests:** Treatment of patients with SYNTHROID requires periodic assessment of adequacy of titration by appropriate laboratory tests and clinical evaluation. Selection of appropriate tests for the diagnosis and management of thyroid disorders depends on patient variables such as presenting signs and symptoms, pregnancy, and concomitant medications. A combination of sensitive TSH assay and free $T_4$ estimate (free $T_4$, free $T_4$ index) are recommended to confirm a diagnosis of thyroid disease. Normal ranges for these parameters are age-specific in newborns and younger children.

TSH alone or initially may be useful for thyroid disease screening and for monitoring therapy for primary hypothyroidism as a linear inverse correlation exists between serum TSH and free $T_4$. Measurement of total serum $T_4$ and $T_3$, resin $T_3$ uptake, and free $T_3$ concentrations may also be useful. Antithyroid microsomal antibodies are an indicator of autoimmune thyroid disease. The presence of positive microsomal antibodies in an euthyroid patient is a major risk factor for the future development of hypothyroidism. An elevated serum TSH in the presence of a normal $T_4$ may indicate subclinical hypothyroidism. Intracellular resistance to thyroid hormone is quite rare, and is suggested by clinical signs and symptoms of hypothyroidism in the presence of high serum $T_4$ levels. Adequacy of SYNTHROID therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring free $T_4$, which should be maintained in the upper half of the normal range. Measurement of TSH is not a reliable indicator of response to therapy for this condition. Adequacy of SYNTHROID therapy for congenital and acquired pediatric hypothyroidism should be assessed by measuring serum total $T_4$ or free $T_4$, which should be maintained in the upper half of the normal range. In congenital hypothyroidism, normalization of serum TSH levels may lag behind normalization of serum $T_4$ levels by 2 to 3 months or longer. In rare patients serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal levels of $T_4$ or free $T_4$.

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

*Levothyroxine sodium absorption*—The following agents may bind and decrease absorption of levothyroxine sodium from the gastrointestinal tract: aluminum hydroxide, cholestyramine resin, colestipol hydrochloride, ferrous sulfate, sodium polystyrene sulfonate, soybean flour (e.g., infant formula), sucralfate.

*Binding to serum proteins*–The following agents may either inhibit levothyroxine sodium binding to serum proteins or alter the concentrations of serum binding proteins: androgens and related anabolic hormones, asparaginase, clofibrate, estrogens and estrogen-containing compounds, 5-fluorouracil, furosemide, glucocorticoids, meclofenamic acid, mefenamic acid, methadone, perphenazine, phenylbutazone, phenytoin, salicylates, tamoxifen.

*Thyroid physiology*–The following agents may alter thyroid hormone or TSH levels, generally by effects on thyroid hormone synthesis, secretion, distribution, metabolism, hormone action, or elimination, or altered TSH secretion: aminoglutethimide, p-aminosalicylic acid, amiodarone, androgens and related anabolic hormones, complex anions (thiocyanate, perchlorate, pertechnetate), antithyroid drugs, β-adrenergic blocking agents, carbamazepine, chloral hydrate, diazepam, dopamine and dopamine agonists, ethionamide, glucocorticoids, heparin, hepatic enzyme inducers, insulin, iodinated cholestographic agents, iodine-containing compounds, levodopa, lovastatin, lithium, 6-mercaptopurine, metoclopramide, mitotane, nitroprusside, phenobarbital, phenytoin, resorcinol, rifampin, somatostatin analogs, sulfonamides, sulfonylureas, thiazide diuretics.

*Adrenocorticoids*–Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients, and may therefore change with changing thyroid status.

*Amiodarone*–Amiodarone therapy alone can cause hypothyroidism or hyperthyroidism.

*Anticoagulants (oral)*–The hypoprothrombinemic effect of anticoagulants may be potentiated, apparently by increased catabolism of vitamin K-dependent clotting factors.

*Antidiabetic agents (insulin, sulfonylureas)*–Requirements for insulin or oral antidiabetic agents may be reduced in hypothyroid patients with diabetes mellitus, and may subsequently increase with the initiation of thyroid hormone replacement therapy.

*β-adrenergic blocking agents*–Actions of some beta-blocking agents may be impaired when hypothyroid patients become euthyroid.

*Cytokines (interferon, interleukin)*–Cytokines have been reported to induce both hyperthyroidism and hypothyroidism.

*Digitalis glycosides*–Therapeutic effects of digitalis glycosides may be reduced. Serum digitalis levels may be decreased in hyperthyroidism or when a hypothyroid patient becomes euthyroid.

*Ketamine*–Marked hypertension and tachycardia have been reported in association with concomitant administration of levothyroxine sodium and ketamine.

*Maprotiline*–Risk of cardiac arrhythmias may increase.

*Sodium iodide ($^{123}I$ and $^{131}I$), sodium pertechnetate Tc99m*–Uptake of radiolabeled ions may be decreased.

*Somatrem/somatropin*—Excessive concurrent use of thyroid hormone may accelerate epiphyseal closure. Untreated hypothyroidism may interfere with the growth response to somatrem or somatropin.

*Theophylline*—Theophylline clearance may decrease in hypothyroid patients and return toward normal when a euthyroid state is achieved.

*Tricyclic antidepressants*—Concurrent use may increase the therapeutic and toxic effects of both drugs, possibly due to increased catecholamine sensitivity. Onset of action of tricyclics may be accelerated.

*Sympathomimetic agents*—Possible increased risk of coronary insufficiency in patients with coronary artery disease.

**Laboratory Test Interactions:** A number of drugs or moieties are known to alter serum levels of TSH, $T_4$ and $T_3$ and may thereby influence the interpretation of laboratory tests of thyroid function (see **Drug Interactions**).

1. Changes in TBG concentration should be taken into consideration when interpreting $T_4$ and $T_3$ values. Drugs such as estrogens and estrogen-containing oral contraceptives increase TBG concentrations. TBG concentrations may also be increased during pregnancy and in infectious hepatitis. Decreases in TBG concentrations are observed in nephrosis, acromegaly, and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroxine-binding-globulinemias have been described. The incidence of TBG deficiency is approximately 1 in 9000. Certain drugs such as salicylates inhibit the protein-binding of $T_4$. In such cases, the unbound (free) hormone should be measured. Alternatively, an indirect measure of free thyroxine, such as the $FT_4I$ may be used.
2. Medicinal or dietary iodine interferes with *in vivo* tests of radioiodine uptake, producing low uptakes which may not indicate a true decrease in hormone synthesis.
3. Persistent clinical and laboratory evidence of hypothyroidism despite an adequate replacement dose suggests either poor patient compliance, impaired absorption, drug interactions, or decreased potency of the preparation due to improper storage.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic $T_4$ is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid hormone therapy and breast cancer has not been confirmed and patients receiving levothyroxine sodium for established indications should not discontinue therapy.

**Pregnancy:** Pregnancy Category A. Studies in pregnant women have not shown that levothyroxine sodium increases the risk of fetal abnormalities if administered during pregnancy. If levothyroxine sodium is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, levothyroxine sodium should be used during pregnancy only if clearly needed.

Thyroid hormones cross the placental barrier to some extent. $T_4$ levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of $T_4$ may not prevent *in utero* hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion and preeclampsia, and has been reported to have an adverse effect on fetal and childhood development. On the basis of current knowledge, SYNTHROID® (levothyroxine sodium, USP) should therefore not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy $T_4$ concentrations may decrease and TSH concentrations may increase to values outside normal ranges. Postpartum values are similar to preconception values. Elevations in TSH may occur as early as 4 weeks gestation.

Pregnant women who are maintained on SYNTHROID should have their TSH measured periodically. An elevated TSH should be corrected by an increase in SYNTHROID dose. After pregnancy, the dose can be decreased to the optimal preconception dose.

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

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