HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIROSINT safely and effectively. See full prescribing information for TIROSINT.

TIROSINT (levothyroxine sodium) capsules, for oral use
Initial U.S. Approval: 2000

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS
See full prescribing information for complete boxed warning
- **Thyroid hormones, including TIROSINT, should not be used for the treatment of obesity or for weight loss.**
- **Doses beyond the range of daily hormonal requirements may produce serious or even life threatening manifestations of toxicity (6, 10).**

INDICATIONS AND USAGE

Levothyroxine sodium is L-thyroxine (T_4) and is indicated for:
- **Hypothyroidism** - As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis (1.1)
- **Pituitary Thyrotropin-Stimulating Hormone (TSH) Suppression** - As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (1.2)

DOSAGE AND ADMINISTRATION

- **Do not cut or crush TIROSINT capsules** (2.1)
- Administer once daily, one-half to one hour before breakfast (2.1)
- Administer at least 4 hours before or after drugs and foods that are known to interfere with absorption (2.1, 7.1, 7.9)
- Starting dose depends on a variety of factors, including age, body weight, cardiovascular status, pregnancy, and concomitant medications (2.2, 2.3)
- The peak therapeutic effect may not be attained for 4-6 weeks (2.2)
- Maintenance dose: Determined with periodic monitoring of TSH and/or T_4 as well as clinical status (2.4)

DOSAGE FORMS AND STRENGTHS

Capsules: 13 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg (3)

CONTRAINDICATIONS

- Patients unable to swallow a capsule, including young children (generally under 6 years of age) (4)
- Acute myocardial infarction (4)
- Uncorrected adrenal insufficiency (4)

WARNINGS AND PRECAUTIONS

- Proper dose titration is critical to prevent the persistence of hypothyroidism or the development of hyperthyroidism (5.1)
- Elderly and patients with cardiovascular disease: Initiate levothyroxine at less than the full replacement dose because of the increased risk of cardiac adverse reactions, including atrial fibrillation (2.3, 5.2, 8.5)
- Suppression of thyroid nodules with levothyroxine is generally not recommended (5.3)
- Patients with concomitant adrenal insufficiency: Treat with replacement glucocorticoids prior to initiation of treatment with levothyroxine (5.4)
- Long-term levothyroxine therapy can decrease bone mineral density. Give the lowest effective dose, particularly in patients with compromised bone mineral density (5.5)

ADVERSE REACTIONS

Common adverse reactions for levothyroxine are primarily those of hyperthyroidism due to therapeutic overdosage including: irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, insomnia, tremors, muscle weakness, change in appetite, weight change, diarrhea, heat intolerance, changes in menstrual periods, and skin rash (6)

To report SUSPECTED ADVERSE REACTIONS, contact Akrimax Pharmaceuticals at 1-888-383-1733, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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 TIROSINT (7)

USE IN SPECIFIC POPULATIONS

Pregnancy may require the use of higher doses of levothyroxine (2.3, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [March 2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS
- **Thyroid hormones, including TIROSINT, 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 *[See Adverse Reactions (6), Drug Interactions (7.7), and Overdosage (10)].***

1 INDICATION AND USAGE

1.1 Hypothyroidism

TIROSINT is indicated as a 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. 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.

1.2 Pituitary Thyrotropin-Stimulating Hormone (TSH) Suppression

TIROSINT is indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Important Information Before Use

Do not cut or crush TIROSINT capsules; capsules should be swallowed whole.
Administer TIROSINT as a single daily dose, preferably one-half to one hour before breakfast. Administer at least 4 hours before or after drugs and foods that are known to interfere with TIROSINT absorption *[See Drug Interactions (7.1, 7.9) and Clinical Pharmacology (12.3)]*.

2.2 Principles of Dosing

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 TIROSINT 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, pregnancy status, concomitant medications, and the specific nature of the condition being treated.
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. Inadequate levothyroxine dosage will fail to ameliorate the signs and symptoms of hypothyroidism *[See Warnings and Precautions (5.1)]*.
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.

2.3 Dosing In Specific Patient Populations

Hypothyroidism in Adults and in Adolescents in Whom Growth and Puberty are Complete
The average full replacement dose of levothyroxine sodium is approximately 1.7 mcg per kg per day (e.g., 100-125 mcg per day for a 70 kg adult). Elderly patients may require less than 1 mcg per kg per day.
The initial levothyroxine dosage is based on the age, weight, and cardiac status of the patient as well as the severity and duration of the hypothyroidism. Therapy may generally begin at full replacement doses in otherwise non-elderly, healthy individuals.
For elderly patients or those with underlying cardiovascular disease, a starting dose of levothyroxine sodium as low as 12.5 mcg per day may be appropriate, with gradual increments in dose at 6-8 week intervals, as needed *[See Warnings and Precautions (5.2)]*. More frequent monitoring is recommended for patients with more severe hypothyroidism.
In general, levothyroxine sodium doses greater than 200 mcg per day are seldom required. An inadequate response to daily doses greater than 300 mcg per day is rare and may indicate poor compliance, malabsorption, and/or drug interactions.
Secondary or Tertiary Hypothyroidism
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 thyroxine (FT_4) level is restored to the upper half of the normal range.
Hypothyroidism (Congenital or Acquired) in the Pediatric Population
Only administer TIROSINT to children who are able to swallow an intact capsule *[See Contraindications (4)]*.
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 Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]*.
Levothyroxine therapy is usually initiated at full replacement doses, with the recommended dose per body weight changing with age (Table 1).

Table 1: Levothyroxine Sodium Dosing Guidelines for Pediatric Hypothyroidism

Age	Daily Dose Per Kg Body Weight[1]
6-12 years	4-5 mcg/kg/day
>12 years but growth and puberty incomplete	2-3 mcg/kg/day
Growth and puberty complete	1.7 mcg/kg/day

[1]The dose should be adjusted based on clinical response and laboratory parameters. *[See Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]*

In children with chronic or severe hypothyroidism, a lower initial dose of 25 mcg per day of levothyroxine sodium is recommended with increasing 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.
Pregnancy
Pregnancy may increase levothyroxine requirements. *[See Use in Specific Populations (8.1)]*
Thyrotropin-Stimulating Hormone (TSH) Suppression in Well-Differentiated Thyroid Cancer
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 less than 0.1 mU per L, and this usually requires a levothyroxine sodium dose of greater than 2 mcg per kg per day. However, in patients with high-risk tumors, the target level for TSH suppression may be less than 0.01 mU per L.
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, thyroid hormone administered intravenously is the recommended route of administration in this rare condition.

2.4 Monitoring TSH and/or Thyroxine (T_4) Levels
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. Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of TIROSINT may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T_4 potency of the drug product.
Adults
In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels alone may be used to monitor therapy. The frequency of TSH monitoring during levothyroxine dose titration depends on the clinical situation but reassessment and titration should be done after an interval of at least 6 weeks after any change in dose. 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 TIROSINT.
Pediatrics
In patients with congenital hypothyroidism, the adequacy of replacement therapy should be assessed by measuring both serum TSH and total or FT_4. 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 T_4 to increase into the upper half of the normal range within 2 weeks of initiation of TIROSINT therapy and/or of the serum TSH to decrease below 20 mU per 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 increasing the dose of TIROSINT.
The recommended frequency of monitoring of TSH and total or FT_4 in children is as follows: at 2 and 4 weeks after the initiation of treatment and following dose stabilization 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 T_4 levels, and a physical examination, if indicated, be performed 2 weeks after any change in TIROSINT dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals *[See Warnings and Precautions (5.1), and Use in Specific Populations (8.4)]*.
Secondary (Pituitary) and Tertiary (Hypothalamic) Hypothyroidism
Adequacy of therapy should be assessed by measuring serum FT_4 levels, which should be maintained in the upper half of the normal range in these patients.

3 DOSAGE FORMS AND STRENGTHS

TIROSINT Capsules: 13 mcg, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg.

TIROSINT Capsules are amber-colored, round/biconvex capsules that contain a viscous amber-colored liquid.

4 CONTRAINDICATIONS

- Do not give TIROSINT to anyone who may be unable to swallow a capsule, including young children (generally under 6 years of age) because of the risk of aspiration.

- Levothyroxine is also contraindicated in patients with:
  - Acute myocardial infarction: administration of levothyroxine in this setting can exacerbate angina and increase the risk of arrhythmia.
  - Uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoid *[See Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Importance of Proper Dose Titration to Prevent Hyperthyroidism or Incomplete Treatment of Hypothyroidism
Levothyroxine has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid hyperthyroidism or incomplete treatment of hypothyroidism. These consequences include, among others, adverse effects on cardiovascular function, growth and development, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Periodic clinical and thyroid function monitoring is recommended *[See Dosage and Administration (2.4)]*. In addition, many drugs interact with levothyroxine sodium necessitating adjustments in dosing to maintain therapeutic response *[See Drug Interactions (7)]*.

5.2 Risk of Cardiac Adverse Reactions in the Elderly and in Patients with Underlying Cardiovascular Disease
In the elderly and in patients with cardiovascular disorders, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease and it should be noted that unlike levothyroxine sodium tablets, TIROSINT capsules cannot be cut in half *[See Dosage and Administration (2.3) and Use in Specific Populations (8.5)]*. If cardiac symptoms develop or worsen, the levothyroxine sodium dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. 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 because of the possibility of precipitating cardiac arrhythmias, including atrial fibrillation. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency *[See Drug Interactions (7.7)]*.

5.3 Patients with Nontoxic Diffuse Goiter or Nodular Thyroid Disease
Suppression of thyroid nodules with levothyroxine is a controversial issue. Routine suppression of benign thyroid nodules is generally not recommended in iodine-sufficient patients. If the serum thyrotropin-stimulating hormone (TSH) is already suppressed, levothyroxine sodium should not be administered. If the serum TSH level is not suppressed, TIROSINT should not be used without frequent laboratory monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential associated adverse cardiovascular signs and symptoms of hyperthyroidism.

5.4 Patients with Concomitant Adrenal Insufficiency
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 *[See Contraindications (4)]*. 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.

5.5 Thyroid Hormone Over-replacement Associated with Decreased Bone Mineral Density
Over-replacement with levothyroxine therapy has been associated with decreased bone mineral density, especially in post-menopausal women. 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, unless TSH suppression is the goal of therapy, as in patients with well-differentiated thyroid cancer.

6 ADVERSE REACTIONS

Common adverse reactions with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage *[See Overdosage (10)]*. 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 (GI)*: diarrhea, vomiting, abdominal cramps, elevations in liver function tests
- *Dermatologic*: hair loss, flushing
- *Endocrine*: decreased bone mineral density
- *Reproductive*: menstrual irregularities, impaired fertility

Adverse Reactions in Children
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.
Hypersensitivity Reactions
Hypersensitivity reactions to inactive ingredients (in this product or other levothyroxine products) 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.

7 DRUG INTERACTIONS

7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics
Many drugs affect thyroid hormone pharmacokinetics (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to TIROSINT. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and actions of other drugs.

A listing of drug interactions with L-thyroxine (T_4) is provided in the following tables. These tables should not be seen as 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., prescribing information of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

Table 2: Drugs That May Decrease T_4 Absorption (Hypothyroidism)
Potential impact: Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism.

Drug or Drug Class	Effect
Calcium Carbonate Ferrous Sulfate	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.
Orlistat	Patients treated concomitantly with orlistat and levothyroxine should be monitored for changes in thyroid function.
Bile Acid Sequestrants -Colesevelam -Cholestyramine -Colestipol Ion Exchange Resins -Kayexalate -Sevelamer	Bile acid sequestrants and ion exchange resins are known to decrease levothyroxine absorption. Administer levothyroxine at least 4 hours prior to these drugs or monitor thyrotropin-stimulating hormone (TSH) levels.
Other drugs: Sucralfate Antacids - Aluminum & Magnesium Hydroxides - Simethicone	

Table 3: Drugs That May Alter T_4 and Triiodothyronine (T_3) Serum Transport Without Effecting Free Thyroxine (FT_4) Concentration (Euthyroidism)

Drugs That May Increase Serum Thyroxine-Binding Globulin (TBG) Concentration	Drugs That May Decrease Serum TBG Concentration
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
Drugs That May Cause Protein-Binding Site Displacement Potential impact: Administration of these agents with levothyroxine results in an initial transient increase in FT_4. Continued administration results in a decrease in serum T_4 and normal FT_4 and TSH concentrations, and patients are likely clinically euthyroid.	

Table 3: Drugs That May Alter T_4 and Triiodothyronine (T_3) Serum Transport Without Effecting Free Thyroxine (FT_4) Concentration (Euthyroidism)

Salicylates (> 2 g/day)	Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total T_4 levels may decrease by as much as 30%.
Other drugs: Furosemide (> 80 mg IV) Heparin Hydantoins Non-Steroidal Anti-inflammatory Drugs - Fenamates - Phenylbutazone	

Table 4: Drugs That May Alter Hepatic Metabolism of T_4 (Hypothyroidism)
Potential impact: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements.

Drug or Drug Class	Effect
Carbamazepine Hydantoins	Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total and FT_4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid. Close monitoring of thyroid hormone parameters is recommended.
Other drugs: Phenobarbital Rifampin	

Table 5: Drugs That May Decrease Conversion of T_4 to T_3
Potential impact: Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased.

Drug or Drug Class	Effect
Beta-adrenergic antagonists (e.g., Propranolol > 160 mg/day)	In patients treated with large doses of propranolol (> 160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state.
Glucocorticoids (e.g., Dexamethasone ≥ 4 mg/day)	Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (See above).
Other: Amiodarone	

7.2 Antidiabetic Therapy
Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.

7.3 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 TIROSINT dose is increased. Coagulation tests should be closely monitored to permit appropriate and timely dosage adjustments.

7.4 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.

7.5 Antidepressant Therapy
Concurrent use of tricyclic (e.g., Amitriptyline) or tetracyclic (e.g., Maprotiline) antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and central nervous system stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.

7.6 Ketamine
Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.

7.7 Sympathomimetics
Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.

7.8 Tyrosine-Kinase Inhibitors
Concurrent use of tyrosine-kinase inhibitors such as imatinib may cause hypothyroidism. TSH levels should be closely monitored in such patients.

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

7.10 Drug-Laboratory Test Interactions
Changes in TBG concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free T_4 index (FT_4I). 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. Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy category A. Levothyroxine 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 thyroxine (T_4) levels may decrease and serum thyrotropin-stimulating hormone (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 TIROSINT should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of TIROSINT. Since postpartum TSH levels are similar to preconception values, the TIROSINT 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.

8.3 Nursing Mothers
Thyroid hormones are excreted only minimally in human milk. Adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

8.4 Pediatric Use
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 (2.2)]*. Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters *[See Warnings and Precautions (5.1)]*
In children in whom a diagnosis of permanent hypothyroidism has not been established, it is recommended that at an appropriate age levothyroxine be discontinued for a trial period. Serum T_4 and TSH levels should be obtained at the end of the trial period, and laboratory test results and clinical assessments should then guide diagnosis and treatment, if warranted.
Rapid restoration of normal serum T_4 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 therapy should be initiated immediately upon diagnosis and is generally continued for life.
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.

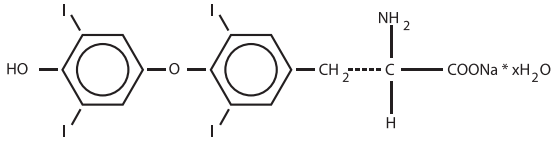
8.5 Geriatric Use
Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose. Atrial fibrillation is a common side effect associated with levothyroxine treatment in the elderly *[See Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.

10 OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism. *[See Warnings and Precautions (5.1) and Adverse Reactions (6)]*. In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures have occurred in a 3-year-old child ingesting 3.6 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.
To obtain up-to-date information about the treatment of overdose, a good resource is the certified Regional Poison Control Center. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in the patient.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's medical status.

11 DESCRIPTION

TIROSINT (levothyroxine sodium) is L-thyroxine. The orally administered gelatin capsules contain synthetic L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T_4 is chemically identical to that produced in the human thyroid gland. Levothyroxine (T_4) sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \bullet x\ H_2O$ (where x = 5), molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:



The inactive ingredients in TIROSINT are gelatin, glycerin and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Thyroid hormones exert their physiologic actions through control of DNA transcription and protein synthesis. Triiodothyronine (T_3) and L-thyroxine (T_4) 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.
The physiological actions of thyroid hormones are produced predominantly by T_3, the majority of which (approximately 80%) is derived from T_4 by deiodination in peripheral tissues.

12.2 Pharmacodynamics
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, T_4 and T_3, by the thyroid gland. Circulating serum T_3 and T_4 levels exert a feedback effect on both TRH and TSH secretion. When serum T_3 and T_4 levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increase.
TSH, along with T_4 levels and other laboratory and clinical data, is primarily used for both the diagnosis of hypothyroidism and evaluation of levothyroxine therapy adequacy *[Dosage and Administration (2.4)]*.
There are drugs known to affect thyroid hormones and TSH levels by various mechanisms. Some drugs may cause a transient decrease in TSH secretion without hypothyroidism: dopamine (≥ 1 mcg per kg per min), glucocorticoids (hydrocortisone ≥ 100 mg per day or equivalent) and octreotide (> 100 mcg per day).

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.

12.3 Pharmacokinetics

Absorption

Absorption of orally administered T_4 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 TIROSINT capsules compared to another marketed levothyroxine sodium tablet, is approximately 103%. T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybeans. Dietary fiber decreases the bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption [See Drug Interactions (7)].

Distribution

Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to T_3. 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 Drug Interactions (7)].

Thyroid hormones do not readily cross the placental barrier [See Use in Specific Populations (8.1)].

Metabolism

T_4 is slowly eliminated. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3, with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (rT_3). T_3 and rT_3 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 T_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

Table 6: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	Half-Life (Days)	Protein Binding (%) [2]
T_4	10 – 20	1	6 – 7 [1]	99.96
T_3	1	4	≤ 2	99.5

T_4: Levothyroxine (L-thyroxine)
T_3: Liothyronine (Triiodothyronine)
[1] 3 – 4 days in hyperthyroidism, 9 – 10 days in hypothyroidism.
[2] Includes TBG, TBPA and TBA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of Levothyroxine Sodium.

13.2 Animal Toxicology and/or Pharmacology

No animal toxicology studies have been conducted with Levothyroxine Sodium.

16 HOW SUPPLIED/STORAGE AND HANDLING

TIROSINT (levothyroxine sodium) capsules are amber-colored, round/biconvex capsules that contain a viscous amber-colored liquid. They are supplied as follows:

Boxes of 28 capsules, consisting of 4 blisters with 7 capsules each. The dosage strength on each box is clearly identified in several locations, and is associated with a distinct color. The color of the circles on the blister is the same color as on the box. Each blister pack contains 7 capsules placed in individual cavities labeled with the dosage strength, the product name (TIROSINT), and an abbreviation for the day of the week on which the capsule is taken.

Do not separate the individual cavities containing the drug from the intact blister as important information may be lost (i.e., manufacturer/distributor names, distributor contact phone number, lot number, and expiration date), and do not remove the individual capsules from blister packaging until ready to use.

Table 7: TIROSINT Packaging Description

Strength (mcg)	Color*	NDC
13	Green	24090-490-84
25	Orange	24090-491-84
50	White	24090-492-84
75	Purple	24090-493-84
88	Olive	24090-494-84
100	Yellow	24090-495-84
112	Rose	24090-496-84
125	Brown	24090-497-84
137	Turquoise	24090-498-84
150	Blue	24090-499-84

*Shown on box and blister packing, not on individual capsules.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. TIROSINT capsules should be protected from heat, light and moisture.

17 PATIENT COUNSELING INFORMATION

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

17.1 Dosing and Administration

- Instruct patients that TIROSINT should only be taken as directed by their healthcare provider.
- Instruct patients to take TIROSINT one-half to one hour before breakfast.
- Instruct patients that TIROSINT capsules should never be crushed or cut.
- Instruct patients to notify their healthcare provider should they become pregnant or are thinking of becoming pregnant while taking TIROSINT. It is likely that the dose of TIROSINT will need to be increased during pregnancy.
- To assist with identifying the name and strength of each TIROSINT capsule, instruct patients not to remove capsules from the blisters in advance, particularly if they are taking multiple strengths.

17.2 Important Information

- Inform patients that it may take several weeks before they notice an improvement in symptoms.
- Inform patients that the levothyroxine in TIROSINT is intended to replace a hormone that is normally produced by the thyroid gland. Generally, replacement therapy is to be taken for life.
- Inform patients that TIROSINT should not be used as a primary or adjunctive therapy in a weight control program.
- Instruct patients to notify their healthcare provider if they are taking any other medications, including prescription and over-the-counter preparations.
- Instruct patients to notify their healthcare provider of any other medical conditions, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems, as the dose of medications used to control these other conditions may need to be adjusted while taking TIROSINT. If patients are taking anticoagulants (blood thinners), their clotting status should be checked frequently.

17.3 Adverse Reactions

- Instruct patients to notify their healthcare provider if they 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.
- Inform patients that partial hair loss may occur rarely during the first few months of TIROSINT therapy; this is usually temporary.

Manufactured for Akrimax Pharmaceuticals, LLC by:
IBSA Institut Biochimique SA
6903 Lugano
Switzerland

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