HYPOTHYROIDISM

Parameters. Inadequate levothyroxine dosage will fail to ameliorate the signs and symptoms of
and adjustments made based on periodic assessment of the patient's clinical response and laboratory
Hence, the following recommendations serve only as dosing guidelines. Dosing must be individualized

The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state.

2.2 Principles of Dosing

Administer at least 4 hours before or after drugs and foods that are known to interfere with TIROSINT
Administer TIROSINT as a single daily dose, preferably one-half to one hour before breakfast.
Do not cut or crush TIROSINT capsules; capsules should be swallowed whole.

TIROSINT is indicated as an adjunct to surgery and radioiodine therapy in the management of
Pituitary Thyrotropin-Stimulating Hormone (TSH) Suppression - As an adjunct to surgery and radioio-
dine therapy in the management of thyrotrpin-dependent well-differentiated thyroid cancer (1.2)

2.1 Important Information Before Use

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

Full Prescribing Information: Contents*

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1.1 Hypothyroidism

1.2 Pituitary TSH Suppression

2 DOSAGE AND ADMINISTRATION

2.1 Important Information Before Use

2.2 Principles of Dosing

2.3 Dosing in Specific Patient Populations

2.4 Monitoring TSH and/or Thyroxine (T4) Levels

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINdications

5 WARNINGS AND PRECAUTIONs

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5.2 Risk of Cardiac Adverse Reactions in the Elderly and in Patients with Underlying Cardiovascular Disease

5.3 Patients with Nontoxic Diffuse Goiter or Nodular Thyroid Disease

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12 CLINICAL PHARMACOLOGY

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13 NONCLINICAL TOXICOLOGY

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13.2 Animal Toxicology and/or Pharmacology

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

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 thyroxi ne (fT3) level is restored to or to a lower level 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.

In general, 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

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily Dose Per Kg Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 years</td>
<td>4-5 mcg/kg/day</td>
</tr>
<tr>
<td>&gt;12 years but growth and puberty incomplete</td>
<td>2.3 mcg/kg/day</td>
</tr>
<tr>
<td>Growth and puberty complete</td>
<td>1.7 mcg/kg/day</td>
</tr>
</tbody>
</table>

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)] Thyrotopin-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 radioactive iodine therapy. Generally, TSH is suppressed to less than 0.1 mU/L, and 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/L per mL Myxedema Coma.

Myxedema coma is a life-threatening emergency characterized by poor circulation and gastrointestinal function, and on glucose and lipid metabolism. Periodic clinical and thyroid function evaluation is recommended in the context of the treatment of patients 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 is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone.

4 Thyroid Hormone Over-replacement Associated with Decreased Bone Mineral Density

Over-replacement with levothyroxine 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 increased excretion of calcium, phosphorus, 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.

ADVERSE REACTIONS

Table 3: Drugs That May Increase Serum Thyroxine-Binding Globulin (TBG) Concentration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>TBG Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofibrate</td>
<td></td>
</tr>
<tr>
<td>Estrone-estriadiol</td>
<td></td>
</tr>
<tr>
<td>Estrogens (oral)</td>
<td></td>
</tr>
<tr>
<td>Hormon / Methadone</td>
<td></td>
</tr>
<tr>
<td>S-Flurouracil</td>
<td></td>
</tr>
<tr>
<td>Mitotane</td>
<td></td>
</tr>
</tbody>
</table>

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 dosing titration is necessary to avoid hyperthyroidism or incomplete treatment of hypothyroidism. These complications include, among others, adverse effects on cardiovascular disease, 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 Cardiac or Other 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 is important to note 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 cardiodysrhythmias develop or worsen while levothyroxine sodium is reduced or withheld for one week, and the patient does not improve, treatment should be continued, and periodic monitoring is required by the physician. Patients with chronic coronary artery disease who are receiving levothyroxine therapy should be monitored during surgical procedures because of the possibility of precipitating cardiac arrhythmias, including atrial fibrillation. Concomitant administration of levothyroxine and sympathomimetic agents in patients with coronary artery disease may precipitate cardiac insufficiency. [See Drug Interactions (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 thyroid-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.
are observed in nephrosis, severe hypoproteinemia, severe liver disease, cirrhosis, and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroid binding globulins 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 (T4) levels may decrease and serum thyrotropin-stimulating hormone (TSH) levels increase to values outside the normal range. Since the thyroid gland of a normal fetus 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 levels, 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 athero-ecetic 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 T4 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 T4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on central nervous 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 closely monitored to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overdoplement may accelerate the bone age and result in premature epiphysial 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 therapy in the elderly (See Dosage and Administration (2.2) 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 Overdose

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 L3,5,3',5'-tetraiodothyronine sodium salt (levothyroxine (T4) sodium). Synthetic T4 is chemically identical to that produced in the human thyroid gland. Levothyroxine (T4) sodium has an empirical formula of C15H14I4NaO6 • x • H2O (where x = 5), molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:

![Image of the structural formula of levothyroxine](image)

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 (T3) and L-thyroxine (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.

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.

#### 12.2 Pharmacodynamics

Thyroid hormone synthesis and secretion is regulated by the hypothalamo-pituitary-thyroid axis. Thyrotrphin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotrphin-stimulating hormone (TSH), from the anterior pituitary. TSH, in turn, is the physiological stimulus for the synthesis and secretion of thyroid hormones, T4 and 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, along with TSH 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 oestrogen (≥ 100 mcg per day).

### Table 3: Drugs That May Alter TI and Triiodothyronine (T3) Serum Transport Without Effecting Free Thyroxine (FT4) Concentration (Euthyroidism)

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates (&gt; 2 g/day)</td>
<td>Salicylates inhibit binding of T3 to TBG and transthyrin. An initial increase in serum FT4 is followed by return of FT4 to normal levels with sustained therapeutic salicylate concentrations, although total T4 levels may decrease by as much as 30%.</td>
</tr>
<tr>
<td>Other drugs:</td>
<td></td>
</tr>
<tr>
<td>Foerumisole (&gt; 80 mg IV)</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Hydantoin</td>
<td></td>
</tr>
<tr>
<td>Non-Toxic Anti-inflammatory Drugs</td>
<td></td>
</tr>
<tr>
<td>- Fenamates</td>
<td></td>
</tr>
<tr>
<td>- Phenylbutazone</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Drugs That May Alter Hepatic Metabolism of T4 (Hypothyroidism)

#### Potential Impact:

- Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements.

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Phenyltoin and carbamazepine reduce serum protein binding of levothyroxine, and total and FT4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.</td>
</tr>
<tr>
<td>Hydantoin</td>
<td>Close monitoring of thyroid hormone parameters is recommended.</td>
</tr>
<tr>
<td>Other drugs:</td>
<td></td>
</tr>
<tr>
<td>Phenobarbitol</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5: Drugs That May Decrease Conversion of T4 to T3

#### Potential Impact:

Administration of these enzyme inhibitors decreases the peripheral conversion of T4 to T3, leading to decreased T3 levels. However, serum T4 levels are usually normal but may occasionally be slightly increased.

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-adrenergic antagonists (e.g., Propranolol &gt; 160 mg/day)</td>
<td>In patients treated with large doses of propranolol (&gt; 160 mg/day), T4 and T3 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.</td>
</tr>
<tr>
<td>Glucocorticoids (e.g., Dexamethasone ≥ 4 mg/day)</td>
<td>Short-term administration of large doses of glucocorticoids may decrease serum T4 concentrations by 30% with minimal change in serum T3 levels. However, long-term glucocorticoid therapy may result in slightly decreased T3 and T4 levels due to decreased TBG production (See above).</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
</tbody>
</table>

### 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 Glycerides

The therapeutic effects of digitalis glycerides may be reduced by levothyroxine. Serum digitalis glyceride levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycerides.

### 7.5 Antidepressant Therapy

Concurrent use of tricyclic (e.g., Amitryptiline) or tetracyclic (e.g., Maprotiline) antidepressants and levothyroxine in patients with coronary artery disease is increased. Coagulation tests should then guide diagnosis and treatment, if warranted.

### 7.6 Ketoamine

Concurrent use may produce marked hypertension and tachycardia; caution 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 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

Changes in TBG concentration must be considered when interpreting FT4 and T3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free T3 index (FT3I). Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations...
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 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 TIROSINT capsules compared to another marketed levothyroxine sodium tablet, is approximately 103%. T4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybeans. Dietary fiber decreases the bioavailability of T4. Absorption may also decrease with age. In addition, many drugs and foods affect T4 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 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 Drug Interactions (7)].

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

T4 is slowly eliminated. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T4 is derived from peripheral T4 by monodeiodination. The liver is the major site of degradation for both T4 and T3, with T4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T4 is deiodinated to yield equal amounts of T3 and reverse T3 (r T3). T3 and r T3 are further deiodinated to diiodothyronines. 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 of T4 is eliminated in the stool. Urinary excretion of T4 decreases with age.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Ratio in Thyroglobulin</th>
<th>Biologic Potency</th>
<th>Half-Life (Days)</th>
<th>Protein Binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>10 – 20</td>
<td>1</td>
<td>6 – 7</td>
<td>99.96</td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>99.5</td>
</tr>
</tbody>
</table>

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 toxicity 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 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 (r T3). T3 and r T3 are further deiodinated to diiodothyronines. 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 of T4 is eliminated in the stool. Urinary excretion of T4 decreases with age.

<p>| Table 6: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients |
|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Ratio in Thyroglobulin</th>
<th>Biologic Potency</th>
<th>Half-Life (Days)</th>
<th>Protein Binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>10 – 20</td>
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</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>99.5</td>
</tr>
</tbody>
</table>

T4: Levothyroxine (L-thyroxine)

T3: Lyothyroxine (Triiodothyronine)

1 3 – 4 days in hyperthyroidism, 9 – 10 days in hypothyroidism.

Table 7: TIROSINT Packaging Description

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

*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 COUNSELLING 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 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.

• Instruct patients that partial hair loss may occur rarely during the first few months of TIROSINT therapy; this is usually temporary.

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