



----- CONTRAINDICATIONS -----

• Uncorrected adrenal insufficiency (4)

----- WARNINGS AND PRECAUTIONS ------

- Cardiac adverse reactions in the elderly and in patients with underlying cardiovascular disease: Initiate TIROSINT at less than the full replacement dose because of the increased risk of cardiac adverse reactions, including atrial fibrillation. (2.3, 5.1, 8.5)
 - Mvxedema coma: Do not use oral thyroid hormone drug products to treat myxedema coma. (5.2) Acute adrenal crisis in patients with concomitant adrenal insufficiency: Treat
- with replacement glucocorticoids prior to initiation of TIROSINT treatment. Prevention of hyperthyroidism or incomplete treatment of hypothyroidism: Proper dose titration and careful monitoring is critical to prevent the
- persistence of hypothyroidism or the development of hyperthyroidism. Worsening of diabetic control: Therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent
- or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing thyroid hormone therapy. (5.5)

 Decreased bone mineral density associated with thyroid hormone overreplacement: Over-replacement can increase bone resorption and decrease bone mineral density. Give the lowest effective dose. (5.6)

----- ADVERSE REACTIONS -----Adverse reactions associated with TIROSINT are primarily those of

loss, diarrhea, heat intolerance, menstrual irregularities, and skin rash (6)

hyperthyroidism due to therapeutic overdosage including: arrhythmias, myocardial infarction, dyspnea, muscle spasm, headache, nervousness, irritability, insomnia, tremors, muscle weakness, increased appetite, weight

To report SUSPECTED ADVERSE REACTIONS, contact IBSA Pharma Inc. at 1-800-587-3513, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- DRUG INTERACTIONS ------

····· USE IN SPECIFIC POPULATIONS ····· Pregnancy may require the use of higher doses of TIROSINT (2.3, 8.1)

See full prescribing information for drugs that 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)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Digitalis Glycosides

Sympathomimetics

Ketamine

Pregnancy

Pediatric Use

Geriatric Use **OVERDOSAGE**

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics NONCLINICAL TOXICOLOGY

16.1 How Supplied

Lactation

DESCRIPTION

Antidepressant Therapy

Tyrosine-Kinase Inhibitors

7.10 Drug-Laboratory Test Interactions USE IN SPECIFIC POPULATIONS

16.2 Storage and Handling
PATIENT COUNSELING INFORMATION

Drug-Food Interactions

7.5

7.7

7.8

7.9

7.10

8.1

8.2

8.4

8.5

10

12

13

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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.

 $\mathsf{TIROSINT}^{\otimes}$ (levothyroxine sodium) capsules, for oral use Initial U.S. Approval: 2000

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.
- serious or even life threatening manifestations of toxicity (6, 10).

Hypothyroidism - As replacement therapy in primary (thyroidal),

- secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism (1)
- Limitations of Use: Not indicated for suppression of benign thyroid nodules and nontoxic
- diffuse goiter in iodine-sufficient patients (1) Not indicated for treatment of transient hypothyroidism during the

- Administer at least 4 hours before or after drugs that are known to
- interfere with absorption (2.1)
- pregnancy), concomitant medications, co-administered food, and the specific nature of the condition being treated. Peak therapeutic effect may not be attained for 4-6 weeks (2.2) See full prescribing information for dosing in specific patient populations
- (2.3)Adequacy of therapy determined with periodic monitoring of TSH and/or
- ----- DOSAGE FORMS AND STRENGTHS ------

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

INDICATIONS AND USAGE DOSAGE AND ADMINISTRATION

General Administration Information

- 2.4 Monitoring TSH and/or Thyroxine (T4) Levels
 DOSAGE FORMS AND STRENGTHS
 CONTRAINDICATIONS
- Cardiac Adverse Reactions in the Elderly and in Patients with
- Underlying Cardiovascular Disease
 - Insufficiency Prevention of Hyperthyroidism or Incomplete Treatment of 5.4
 - Hypothyroidism
 - Decreased Bone Mineral Density Associated with Thyroid

Drugs Known to Affect Thyroid Hormone Pharmacokinetics Antidiabetic Therapy

- **FULL PRESCRIBING INFORMATION**
- listed. TSH Suppression in Well-Differentiated Thyroid Cancer Generally, TSH is suppressed to below 0.1 mIU per Liter, and this usually requires a TIROSINT dose of greater than 2 mcg per kg pe

day. However, in patients with high-risk tumors, the target level for

2.4 Monitoring TSH and/or Thyroxine (T4) Levels
Assess the adequacy of therapy by periodic assessment of laboratory

tests and clinical evaluation. Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of TIROSINT may be evidence of inadequate absorption, poor

TSH suppression may be lower

compliance, drug interactions, or a combination of these factors. In adult patients with primary hypothyroidism, monitor serum TSH levels after an interval of 6 to 8 weeks after any change in dose. In patients on a stable and appropriate replacement dose, evaluate

of replacement therapy by measuring both serum TSH and total or

free-T4. Monitor TSH and total or free-T4 in children is as follows: at 2 and 4 weeks after the initiation of treatment 2 weeks after any change in dosage, and then every 3 to 12 months thereafter following dose

clinical and biochemical response every 6 to 12 months and whenever there is a change in the patient's clinical status. In patients with congenital hypothyroidism, assess the adequacy

stabilization until growth is completed. Poor compliance or abnormal values may necessitate more frequent monitoring. Perform routine clinical examination, including assessment of mental and physical growth and development, and bone maturation at regular intervals. While the general aim of therapy is to normalize the serum TSH level, TSH may not normalize in some patients due to *in utero* hypothyroidism causing a resetting of the pituitary-thyroid feedback. Failure of the serum T4 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 mIU per Liter within 4 weeks may indicate the child is not receiving adequate therapy. Assess compliance, dose of medication administered, and method of administration prior to increasing the dose of TIROSINT [see Warnings and Precautions (5.4) and Use in Specific Populations (8.4)]. Secondary (Pituitary) and Tertiary (Hypothalamic) Hypothyroidism Monitor serum free-T4 levels maintain in the upper half of the normal range in these patients. DOSAGE FORMS AND STRENGTHS

TIROSINT capsules are amber-colored, round/biconvex capsules imprinted with a dosage strength specific letter on one side and $\,$ containing a viscous amber-colored liquid and are available as follows:

Imprint Code

Α

Н

Strength (mcg)

13

75

25 E 50 <u>G</u>

	_			
88	Ī			
100	<u>K</u>			
112	<u>M</u>			
125	N			
137	P			
150	<u>s</u>			
175	<u>U</u>			
200	Y			
4 CONTRAINDICATIONS TIROSINT is contraindicated in patients with uncorrected adrenal insufficiency [see Warnings and Precautions (5.3)].				
5 WARNINGS AND PRECAUTIONS				
5.1 Cardiac Adverse Reactions in the Elderly and in Patients with				

Underlying Cardiovascular Disease

Overtreatment with levothyroxine may cause an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias, particularly in patients with cardiovascular disease and in elderly patients. Initiate TIROSINT therapy in this population at lower doses than those recommended in younger individuals or in patients without cardiac disease [see Dosage and Administration (2.3) and Use in Specific Populations (8.5)].

Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive TIROSINT therapy. Monitor patients receiving concomitant TIROSINT and sympathomimetic agents for signs and symptoms of coronary insufficiency. If cardiac symptoms develop or worsen, reduce the TIROSINT dose or withhold it for one week and restart at a lower

Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable

5.3 Acute Adrenal Crisis in Patients with Concomitant Adrenal Insufficiency

Thyroid hormone increases metabolic clearance of glucocorticoids. Initiation of thyroid hormone therapy prior to initiating glucocorticoid therapy precipitate an acute adrenal crisis in patient with adrenal insufficiency. Treat patients with adrenal insufficiency with replacement glucocorticoids prior to initiating treatment with TIROSINT [see Contraindications (4)]. 5.4 Prevention of Hyperthyroidism or Incomplete Treatment of

Hypothyroidism TIROSINT has a narrow therapeutic index. Over- or undertreatment with TIROSINT may have negative effects on growth and

development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Titrate the dose of TIROSINT carefully and monitor response to titration to avoid these effects [see Dosage and Administration (2.4)]. Monitor for the presence of drug or food interactions when using TIROSINT and adjust the dose as necessary [see Drug Interactions (7) and Clinical Pharmacology (12.3)]. 5.5 Worsening of Diabetic Control

may worsen glycemic control and result in increased antidiabetic starting, changing, or discontinuing thyroid hormone therapy [see 5.6 Decreased Bone Mineral Density Associated with Thyroid Hormone Over-Replacement Increased bone resorption and decreased bone mineral density may occur as a result of levothyroxine over-replacement, particularly

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. Administer the minimum dose of TIROSINT that achieves the desired clinical and biochemical response to mitigate against this risk. ADVERSE REACTIONS

Adverse reactions associated with TIROSINT therapy are primarily

those of hyperthyroidism due to therapeutic overdosage [see Warnings and Precautions (5) and Overdosage (10)]. They include the

General: fatigue, increased appetite, weight loss, heat intolerance,

- anxiety, irritability, emotional lability, insomnia Musculoskeletal: tremors, muscle weakness, muscle spasm Cardiovascular: palpitations, tachycardia, arrhythmias, increa
- 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, rash Endocrine: decreased bone mineral density

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility HOW SUPPLIED/STORAGE AND HANDLING

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

- Reproductive: menstrual irregularities, impaired fertility
 Seizures have been reported rarely with the institution of levothyroxine
- 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. Hypersensitivity Reactions

Ferrous Sulfate

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

7.1 Drugs Known to Affect Thyroid Hormone Pharmacokinetics Many drugs can exert effects thyroid hormone pharmacokinetics (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to TIROSINT (see Tables 2 to 5 below).

Table 2: Drugs That May Decrease T4 Absorption (Hypothyroidism)

Potential impact: Concurrent use may reduce the efficacy of TIROSINT by binding and delaying or preventing absorption, potentially resulting in hypothyroidism

Drug or Drug Class Calcium carbonate may an insoluble chelate Calcium Carbonate

with

an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer TIROSINT at least 4 hours apart from these agents.
Monitor patients treated concomitantly with orlistat and TIROSINT for changes in thyroid function.
Bile acid sequestrants and ion exchange resins are known to decrease levothyroxine absorption. Administer TIROSINT at least 4 hours prior to these drugs or monitor thyrotropin (TSH) levels.
Gastric acidity is an essential requirement for adequate absorption of levothyroxine. Sucralfate, antacids and proton pump inhibitors may cause hypochlorhydria, affect intragastric pH, and reduce levothyroxine absorption. Monitor patients appropriately

serum thyroxine-binding globulin (TBG) concentration contraceptives Estrogens (oral) Heroin / Methadone

Drug or Drug Class

Estrogen-containing oral

Clofibrate

Effect

in serum FT4

These drugs may increase

5-Fluorouracil Mitotane Tamoxifen		
Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid	These drugs may decrease serum TBG concentration.	
Potential impact (below): Admini TIROSINT results in an initial trans administration results in a decrease TSH concentrations.	ient increase in FT4. Continued	
Salicylates (> 2 g/day)	Salicylates inhibit binding of T4 and T3 to TBG and transthyretin. An initial	

followed by return of FT4 to normal levels with sustained therapeutic serum salicylate concentrations, although total T4 levels may decrease by as much as 30%.

the protein binding of T4 to TBG and albumin, causing an increased free-T4 fraction in serum. Furosemide compete for T4-binding sites on TBG, prealbumin, and albumin, so that a single high dose can acutely lower the total T4 level

Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total and free-T4 may be reduced by 20% to 40%, but most patients and are clinically euthyroid. Closely monitor thyroid hormone parameters Potential impact: Stimulation of hepatic microsomal drug-

These drugs may cause protein-binding site

displacement. Furosemide has been shown to inhibit

requirements. Drug or Drug Class

Phenobarbital to reduce the response to Rifampin thyroxine. Phenobarbital increases L-thyroxine metabolism by inducing uridine 5'-diphosphoalucuronosyltransferase (LIGT) and leads to a lower T4 serum levels. Changes in thyroid status may occur if barbiturates are added or treated for hypothyroidism. Rifampin has been shown to

WARNING: NOT FOR TREATMENT OF OBESITY or FOR WEIGHT LOSS

Doses beyond the range of daily hormonal requirements may produce

- ------ INDICATIONS AND USAGE ------
- TIROSINT is L-thyroxine (T4) indicated for adults and pediatric patients 6 years and older with:
- Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression -As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (1)
- recovery phase of subacute thyroiditis (1)
- ----- DOSAGE AND ADMINISTRATION -----Administer once daily, on an empty stomach, one-half to one hour before
- breakfast (2.1)
- Evaluate the need for dose adjustments when regularly administering within an hour of certain foods that may affect TIROSINT absorption (2.1) Swallow TIROSINT capsules whole, do not cut, crush, or chew (2.1) Starting dose depends on a variety of factors, including age, body
- weight, cardiovascular status, concomitant medical conditions (including
- T4 as well as clinical status (2.4)

Capsules: 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg (3)

- General Principles of Dosing Dosing in Specific Patient Populations 2.3
- WARNINGS AND PRECAUTIONS
- - Myxedema Coma Acute Adrenal Crisis in Patients with Concomitant Adrenal
 - Worsening of Diabetic Control
- Hormone Over-replacement ADVERSE REACTIONS **DRUG INTERACTIONS**
- 7.3 Oral Anticoagulants
- 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)]. INDICATION AND USAGE

Hypothyroidism TIROSINT is indicated as a replacement therapy in adults and

pediatric patients 6 years and older with primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH)

SuppressionTIROSINT is indicated as an adjunct to surgery and radioiodine therapy

in the management of adults and pediatric patients 6 years and olde with thyrotropin-dependent well-differentiated thyroid cancer.

TIROSINT is not indicated for treatment of transient hypothyroidism during the recovery phase of subacute thyroiditis.

stomach, one-half to one hour before breakfast.

TIROSINT is not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients as there are no clinical benefits and overtreatment with TIROSINT may induce hyperthyroidism [see Warnings and Precautions (5.4)].

DOSAGE AND ADMINISTRATION General Administration Information Administer TIROSINT as a single daily oral dose, on an empty

Administer TIROSINT at least 4 hours before or after drugs known to interfere with TIROSINT absorption [see Drug Interactions (7.1)]

Evaluate the need for dose adjustments when regularly administering within an hour of certain foods that may affect TIROSINT absorption [see Drug Interactions (7.9) and Clinical Pharmacology (12.3)]. Swallow TIROSINT capsules whole, do not cut, crush, or chew. 2.2 General Principles of Dosing

The dose of TIROSINT for hypothyroidism or pituitary TSH suppression depends on a variety of factors including the patient's

age, body weight, cardiovascular status, concomitant medical

conditions (including pregnancy), concomitant medications, co-administered food, and the specific nature of the condition being treated [see Dosage and Administration (2.3), Warnings and Precautions (5), and Drug Interactions (7)]. Dosing must be individualized to account for these factors and dose adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters [see Dosage and Administration (2.4)]. The peak therapeutic effect of a given dose of TIROSINT may not be attained for 4 to 6 weeks. 2.3 Dosing In Specific Patient Populations Primary Hypothyroidism in Adults and in Adolescents in Whom Growth and Puberty are Complete Start TIROSINT at the full replacement dose in otherwise healthy, non-elderly individuals who have been hypothyroid for only a short

day is rare and may indicate poor compliance, malabsorption, drug interactions, or a combination of these factors.

For elderly patients or patients with underlying cardiovascular disease, start with a dose of 12.5 to 25 mcg per day. Increase the dose every 6 to 8 weeks, as needed, until the patient is clinically euthyroid and the serum TSH returns to normal. The full replacement dose of TIROSINT may be less than 1 mcg per kg per day in elderly patients. In patients with severe longstanding hypothyroidism, start with a dose of 12.5 to 25 mcg per day. Adjust the dose in 12.5 to 25 mcg

increments every 2 to 4 weeks until the patient is clinically euthyroid and the serum TSH level is normalized.

time (such as a few months). The average full replacement dose of TIROSINT is approximately 1.6 mcg per kg per day (for example: 100-125 mcg per day for a 70 kg adult).

Adjust the dose by 12.5 to 25 mcg increments every 4 to 6 weeks until the patient is clinically euthyroid and the serum TSH returns to normal. Doses greater than 200 mcg per day are seldom required. An inadequate response to daily doses greater than 300 mcg per

Secondary or Tertiary Hypothyroidism Start TIROSINT at the full replacement dose in otherwise healthy, Start TIROSINI at the full replacement dose in otherwise healthy, non-elderly individuals. Start with a lower dose in elderly patients with underlying cardiovascular disease or patients with severe longstanding hypothyroidism as described above. Serum TSH is not a reliable measure of TIROSINT dose adequacy in patients with secondary or tertiary hypothyroidism, and should not be used to monitor therapy. Use the serum free-T4 level to monitor adequacy of therapy in this patient population. Titrate TIROSINT dosing per above instructions

until the patient is clinically euthyroid and the serum free-T4 level is restored to the upper half of the normal range.

Pediatric Dosage - Congenital or Acquired Hypothyroidism Only administer TIROSINT to pediatric patients 6 years and older who

are able to swallow an intact capsule.

The recommended daily dose of TIROSINT in pediatric patients

with hypothyroidism is based on body weight and changes with age as described in Table 1. Start TIROSINT at the full daily dose in most pediatric patients. Start at a lower dose in children at risk for hyperactivity (see below). Monitor for clinical and laboratory response [see Dosage and Administration (2.4)]. Table 1: TIROSINT Dosing Guidelines for Pediatric Hypothyroidism

Age

6-12 years

Greater than 12 years

in Specific Populations (8.4)].

but growth and puberty incomplete Growth and puberty 1.6 mcg/kg/day complete

^a The dose should be adjusted based on clinical response and laboratory parameters [see Dosage and Administration (2.4) and Use

Daily Dose Per Kg Body Weight^a

4-5 mcg/kg/day

2-3 mcg/kg/day

Children at risk for hyperactivity: To minimize the risk of hyperactivity in children, start at one-fourth the recommended full replacement dose, and increase on a weekly basis by one-fourth the full-recommended replacement dose until the full recommended replacement dose is reached. Pregnancy Preexisting Hypothyroidism: TIROSINT dose requirements may increase during pregnancy. Measure serum TSH and free-T4 as soon as pregnancy is confirmed and, at a minimum, during each trimester

of pregnancy. In patients with primary hypothyroidism, maintain serum TSH in the trimester-specific reference range. For patients with

serum TSH above the normal trimester specific range, increase the dose of TIROSINT by 12.5 to 25 mcg per day and measure TSH every four weeks until a stable TIROSINT dose is reached and serum TSH is

weight per day. Evaluate serum TSH every 4 weeks and adjust

specific range [see Use in Specific Populations (8.1)].

TIROSINT dosage until serum TSH is within the normal trimester

within the normal trimester specific range. Reduce TIROSINT dosage to pre-pregnancy levels immediately after delivery and measure serum TSH levels 4 to 8 weeks postpartum to ensure the TIROSINT dose is New Onset Hypothyroidism: Normalize thyroid function as rapidly as possible. In patients with moderate to severe signs and symptoms of hypothyroidism, start TIROSINT at the full replacement dose (1.6 mcg per kg body weight per day). In patients with mild hypothyroidism (TSH < 10 mIU per Liter), start TIROSINT at 1.0 mcg per kg body

absorption of levothyroxine sodium from the gastrointestinal tract. Use of oral thyroid hormone drug products is not recommended to treat myxedema coma. Administer thyroid hormone products formulated for intravenous administration to treat myxedema coma. Other drugs: Carbamazepine Furosemide (> 80 mg IV) **Heparin** . Hydantoins Non-Steroidal Anti-inflammatory Drugs Fenamates

Addition of levothyroxine therapy in patients with diabetes mellitus agent or insulin requirements. Carefully monitor glycemic control after

fever, excessive sweating Central nervous system: headache, hyperactivity, nervousness,

Table 4: Drugs That May Alter Hepatic Metabolism of T4

metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased TIROSINT Phenobarbital has been shown

accelerate the metabolism of levothyroxine.

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.			
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), T3 and T4 levels change, TSH levels remain normal, and patients are clinically euthyroid. 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 T3 concentrations by 30% with minimal change in serum T4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T3 and T4 levels due to decreased TBG production (see Table 3 above).		
Other: Amiodarone	Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, and decrease or normal free-T3) in clinically euthyroid patients.		

7.2 Antidiabetic Therapy Addition of TIROSINT therapy in patients with diabetes mellitus may

worsen glycemic control and result in increased antidiabetic age or insulin requirements. Careful monitor glycemic control, especially when thyroid therapy is started, changed, or discontinued [see Warnings and Precautions (5.5)].

7.3 Oral Anticoagulants

TIROSINT 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. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

digitalis glycosides.

7.4 Digitalis GlycosidesTIROSINT may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may decrease when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of 7.5 Antidepressant Therapy

Concurrent use of tricyclic (e.g., Amitriptyline) or tetracyclic (e.g.,

Maprotiline) antidepressants and TIROSINT 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. TIROSINT may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on TIROSINT may result in increased TIROSINT requirements.

7.6 Ketamine Concurrent use of ketamine and TIROSINT may produce marked

hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients. 7.7 Sympathomimetics

Concurrent use of sympathomimetics and TIROSINT 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. Closely monitor TSH levels in such patients.

7.9 Drug-Food Interactions Consumption of certain foods may affect TIROSINT absorption thereby necessitating adjustments in dosing [see Dosage and

Administration (2.1)]. Soybean flour (infant formula), cottonseed meal, walnuts, and dietary fiber may bind and decrease the absorption of TIROSINT from the GI tract. Grapefruit juice may delay the absorption of levothyroxine and reduce its bioavailability. 7.10 Drug-Laboratory Test Interactions

Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone

and/or determine the free T4 index (FT4I) in this circumstance Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, androgens and corticosteroids decrease TBG concentration. Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Experience with levothyroxine use in pregnant women, including

data from post-marketing studies, have not reported increased rates of major birth defects or miscarriages [see Data]. There are risks to the mother and fetus associated with untreated hypothyroidism in pregnancy. Since thyroid-stimulating hormone (TSH) levels may increase during pregnancy, TSH should be monitored and TIROSINT dosage adjusted during pregnancy [see Clinical Considerations]. There are no animal studies conducted with levothyroxine during pregnancy. TIROSINT should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general

population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk

Maternal hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, gestational hypertension, pre-eclampsia, stillbirth, and premature delivery.
Untreated maternal hypothyroidism may have an adverse effect on fetal neurocognitive development Dose Adjustments During Pregnancy and the Postpartum Period Pregnancy may increase TIROSINT requirements. Serum TSH level

should be monitored and the TIROSINT dosage adjusted during pregnancy. Since postpartum TSH levels are similar to preconception values, the TIROSINT dosage should return to the pre-pregnancy dose immediately after delivery[see Dosage and Administration (2.3)].

Human Data Levothyroxine is approved for use as a replacement therapy for

TIROSINT?

hypothyroidism. There is a long experience of levothyroxine use in pregnant women, including data from post-marketing studies that have not reported increased rates of fetal malformations, miscarriages or other adverse maternal or fetal outcomes associated with levothyroxine use in pregnant women.

not produce enough of this hormone.

8.2 Lactation

Limited published studies report that levothyroxine is present in human milk. However, there is insufficient information to determine the effects of levothyroxine on the breastfed infant and no available information on the effects of levothyroxine on milk production. Adequate levothyroxine treatment during lactation may normalize milk production in hypothyroid lactating mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TIROSINT and any potential adverse effects on the breastfed infant from TIROSINT or from the underlying

8.4 Pediatric Use TIROSINT is indicated for use in pediatric patients 6 years and older. The initial dose of TIROSINT varies with age and body weight. Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters [see Dosage and Administration

In children in whom a diagnosis of permanent hypothyroidism has not been established, discontinue TIROSINT administration for a trial period. Obtain serum T4 and TSH levels at the end of the trial period, and use laboratory test results and clinical assessments to guide diagnosis and treatment, if warranted. Congenital Hypothyroidism [see Dosage and Administration (2.3, 2.4)]

Rapid restoration of normal serum T4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism or intellectual development as well as on overall physical growth and maturation. Therefore, initiate levothyroxine therapy immediately upon diagnosis. Levothyroxine is generally continued for life in these

Closely monitor children during the first two weeks of TIROSINT therapy for cardiac overload and arrhythmias.

Closely monitor patients to avoid undertreatment and overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult

Acquired Hypothyroidism in Pediatric Patients Closely monitor patients 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, initiate TIROSINT therapy at less than the full replacement dose [see Warnings and Precautions (5.1) and Dosage and

Atrial fibrillation is the most common of the arrhythmias observed with levothyroxine overtreatment in the elderly. 10 OVERDOSAGE The signs and symptoms of overdosage are those of hyperthyroidism [see Warnings and Precautions (5) and Adverse Reactions (6)]. In

Administration (2.3)]. Atrial arrhythmias can occur in elderly patients

addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures 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. Reduce the TIROSINT dose or discontinue temporarily if signs or

symptoms of overdosage occur. Initiate appropriate supportive treatment as dictated by the patient's medical status. For current information on the management of poisoning or overdosage, contact the National Poison Control Center 1-800-222-1222 or www.poison.org.

TIROSINT (levothyroxine sodium) capsules for oral use contain synthetic L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T4 is chemically identical to that produced in the human thyroid Bland. Levothyroxine (T4) sodium has an empirical formula of the California Bland. formula of $C_{15}H_{10}I_4NNaO_4$ • 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

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.

Oral levothyroxine sodium is a synthetic T4 hormone that exerts the same physiologic effect as endogenous T4, thereby maintaining normal T4 levels when a deficiency is present.

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. 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 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 (see Table 6). The major pathway of thyroid hormone metabolism is through sequential deiodination. thyroid normone metabolism is through sequential delodination. Approximately 80% of circulating T3 is derived from peripheral T4 by monodeiodination. The liver is the major site of degradation for both T4 and T3, with T4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T4 is deiodinated to yield equal amounts of T3 and reverse T3 (rT3). T3 and rT3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T4 is eliminated in the stool. Urinary excretion of T4 decreases with age.

Table 6: Pharmacokinetic Parameters of Thyroid Hormones in

Euthyroid Patients					
Hormone	Ratio in Thyroglobulin	Biologic Potency	Half-Life (Days)	Protein Binding (%) ^a	
Levothyroxine (T4)	10 – 20	1	6 – 7 ^b	99.96	
Liothyronine (T3)	1	4	≤ 2	99.5	

¹³ NONCLINICAL TOXICOLOGY

Includes TBG, TBPA and TBA.

 $^{\rm b}$ 3 – 4 days in hyperthyroidism, 9 – 10 days in hypothyroidism.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

TIROSINT (levothyroxine sodium) capsules are amber-colored, round/

biconvex capsules, imprinted with a dosage strength specific letter on one side and containing a viscous amber-colored liquid. They are supplied as follows:

Table 7: TIROSINT Packaging Description - Boxes of 30 capsules, consisting of 3 blisters with 10 capsules each Strength Color* Imprint NDC

(mcg)		Code		
13	Green	<u>A</u>	71858-0005-4	
25	Orange	E	71858-0010-4	
50	White	G	71858-0015-4	
75	Purple	Н	71858-0020-4	
88	Olive	ī	71858-0025-4	
100	Yellow	K	71858-0030-4	
112	Rose	<u>M</u>	71858-0035-4	
125	Brown	<u>N</u>	71858-0040-4	
137	Turquoise	<u>P</u>	71858-0045-4	
150	Blue	<u>s</u>	71858-0050-4	
175	Lilac	ū	71858-0055-4	
200	Pink	Y	71858-0060-4	

^{*}Shown on box and blister packing, not on individual capsules. The dosage strength on each box is clearly identified in several locations, and is associated with a distinct color. The color of the

contains 10 capsules placed in individual cavities labeled with the dosage strength and the product name (TIROSINT). 16.2 Storage and Handling Store at 25° C (77° F); excursions permitted to 15° - 30° C (59- 86° F) [see USP Controlled Room Temperature]. TIROSINT capsules should be

circles on the blister is the same color as on the box. Each blister pack

protected from heat, light and moisture.

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.

17 PATIENT COUNSELING INFORMATION Advise the patient and/or the caregiver to read the FDA-approved Dosing and Administration

patient labeling (Patient Information Sheet).

Instruct patients to take TIROSINT only as directed by their Instruct patients to take TIROSINT one-half to one hour before

- Inform patients that agents such as iron and calcium supplements and antacids can decrease the absorption of levothyro Instruct patients not to take TIROSINT within 4 hours of these
- Instruct patients that TIROSINT capsules should be swallowed whole and never be cut, crushed, or chewed. 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. Instruct patients to notify their healthcare provider should they
- become pregnant or are thinking of becoming pregnant while taking TIROSINT. 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 [see Drug Interactions (7)]. 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 they have diabetes, instruct patients to monitor their blood and/or urinary glucose levels as directed by their physician and immediately report any changes to their physician. If patients are taking anticoagulants, their clotting status should be checked frequently. Instruct patients to notify their physician or dentist that they are taking TIROSINT prior to any surgery.
- 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 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, but this is usually temporary.

IBSA Pharma Inc

IBSA Institut Biochimique SA 6915 Pambio-Noranco Parsippany, NJ 07054 Switzerland

Manufactured for IBSA Pharma Distributed by:

capsules, for oral use What is the most important information I should know about

PATIENT INFORMATION

TIROSINT® [tee-row-sent]

(levothyroxine sodium)

• Do not use TIROSINT to treat weight problems or weight loss.

• Do not take more TIROSINT than your doctor prescribes for you to take. Over dosage or taking too much TIROSINT may cause life-threatening side effects or death.

What is TIROSINT? TIROSINT is a prescription medicine that contains a hormone called levothyroxine which is normally produced by the thyroid gland. TIROSINT is used to treat adults and children 6 years of age or older:

• to replace or give extra levothyroxine in people whose thyroid does

thyroid cancer called thyroid-dependent well-differentiated thyroid

TIROSINT should not be used to treat people who are recovering from swelling of the thyroid gland (thyroiditis) and whose bodies do not produce enough levothyroxine for a short time.

TIROSINT is unsuitable for children less than 6 years of age or who

who need surgery and radioiodine therapy to manage a type of

may be unable to swallow an intact capsule. Do not take TIROSINT: if your adrenal glands are not working well and you have not been

Before you take TIROSINT, tell your doctor about all of your medical conditions, including if you: • have or had heart problems.

treated for this problem.

 have a low red blood cell count (anemia). have diabetes. • have weak bones (osteoporosis).

have or had thyroid nodules.

• have any food or drug allergies.

- have or had a history of blood clotting problems.
- have recently received radiation therapy with iodine (such as I-131). are pregnant or plan to become pregnant. TIROSINT may harm your
- unborn baby. Your doctor may need to change your TIROSINT dose while you are pregnant. • are breastfeeding. TIROSINT can pass into your milk. Talk to your

have kidney or pituitary gland problems.

- doctor about the best way to feed your baby if you take TIROSINT. Tell your doctor about all the medicines you take including
- prescription and over-the-counter medicines, vitamins, and herbal supplements. TIROSINT may affect the way other medicines work, and other medicines may affect how TIROSINT works. You can ask your doctor or pharmacist for a list of medicines that interact with
- How should I take TIROSINT? Take TIROSINT exactly as your doctor tells you to take it.

different medicine.

Your doctor will tell you how much TIROSINT to take each day. Swallow TIROSINT capsules whole. Do not cut, crush, or chew

calcium carbonate or iron (ferrous sulfate).

 Your doctor may change your dose, if needed. Take your dose of TIROSINT 1 time each day, 30 minutes to 1 hour before breakfast, on an empty stomach. • Certain medicines can interfere with how TIROSINT is absorbed by your body. Take TIROSINT:

TIROSINT capsules before swallowing. If you or your child cannot

swallow TIROSINT capsules whole, tell your doctor. You may need a

sequestrants or ion exchange resins. Know the medicines that you take. Ask your doctor or pharmacist for a list of these medicines, if you are not sure. Certain foods including soybean flour, cotton seed meal, walnuts,

o at least 4 hours before or after you take medicines that contain

o at least 4 hours before you take medicines that contain bile acid

- and dietary fiber can affect your treatment and dose of TIROSINT. Talk to your doctor if you eat or drink these foods. Do not remove TIROSINT capsules from the original blister package until you are ready to take them. Your doctor should do certain blood tests while you are taking TIROSINT and may change your daily dose of TIROSINT as needed.
- You should not stop taking TIROSINT or change your dose unless your doctor tells you to. It may take weeks before you notice your symptoms getting better.
- Keep using this medicine even if you feel well. • If you take too much TIROSINT or overdose, call your doctor or poison control center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

chest pain and irregular heartbeat. Your risk of developing heart problems may be greater if you are elderly, have heart problems, or if you take too much TIROSINT. Your doctor may reduce your dose

What are the possible side effects of TIROSINT?

TIROSINT may cause serious side effects, including:

or stop treatment with TIROSINT for a while if you develop heart worsening diabetic control. If you are diabetic, it may be harder to control your blood sugar levels causing hyperglycemia while taking TIROSINT. Check your blood sugar levels closely after starting, changing, or stopping treatment with TIROSINT. Your doctor may have to change your diabetes treatment plan.

heart problems. You may experience an increased heart rate,

- weak or brittle bones. Your risk of developing weak or brittle bones may be greater if you are post-menopausal or you take too much TIROSINT. The most common side effects of TIROSINT include: • irregular heartbeat
- chest pain shortness of breath leg cramps
- headache
 - muscle weakness change in appetite

weight loss

irritability

nervousness

sleep problems (insomnia)

- vomiting diarrhea
- sweating a lot heat intolerance
- changes in menstrual period hives or skin rash

fever

- Other side effects may include: partial hair loss during the first months of treatment with TIROSINT.
- These are not all the possible side effects of TIROSINT. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- 1-800-587-3513 or www.fda.gov/medwatch. How should I store TIROSINT?
- Store TIROSINT at room temperature between 68°F to 77°F (20°C to 25°C) Store TIROSINT away from heat, light, and moisture. Keep TIROSINT in the original blister pack until you are ready to use

Keep TIROSINT and all medicines out of the reach of children. General information about the safe and effective use of TIROSINT

This usually lasts a short period of time (temporary)

You may also report side effects to IBSA Pharma Inc. at

listed in a Patient Information leaflet. Do not use TIROSINT for a condition for which it was not prescribed. Do not give TIROSINT to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about TIROSINT that is written for health professionals. What are the ingredients in TIROSINT?

Medicines are sometimes prescribed for purposes other than those

Inactive ingredients: gelatin, glycerin, and water Manufactured by: IBSA Institut Biochimique SA, 6915 Pambio-Noranco,

Active ingredient: levothyroxine sodium

Marketed and distributed by: IBSA Pharma Inc., Parsippany, NJ 07054 USA For more information, go to www.tirosint.com or call 1-800-587-3513.

This Patient Information has been approved by the U.S. Food and Drug Administration