TIROSINT® (levothyroxine sodium) capsules Rx only

DESCRIPTION
TIROSINT (levothyroxine sodium) capsules are soft gelatin capsules to be orally administered, which contain synthetic L,3,5,3',5'-tetraiodothyronine sodium salt (levothyroxine (T4) sodium). Synthetic T4 is identical to that produced in the human thyroid gland. Levothyroxine (T4) sodium has an empirical formula of C15H10I4NNaO4 • x • H2O (where x = 5), molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:

\[
\text{HO} \quad \text{NH}_2 \\
\text{CH}_3 \quad \text{COONa} \quad * \quad \text{x} \quad \text{H}_2\text{O}
\]

Inactive Ingredients: gelatin, gelatin, and water.

CLINICAL PHARMACOLOGY
Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin-stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyroxine (T4) and L-triiodothyronine (T3), by the thyroid gland. Circulating serum T4 and T3 levels exert a feedback effect on both TRH and TSH secretion. When serum T4 and T3 levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increases.

The mechanisms by which thyroid hormones exert their physiologic actions are not completely understood, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T4 and T3 diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. The thyroid hormone receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates, and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development.

The physiologic actions of thyroid hormones are produced predominantly by T4, the majority of which (approximately 80%) is derived from T3 by deiodination in peripheral tissues. Levothyroxine, at doses individualized according to patient response, is effective as replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Levothyroxine is also effective in the suppression of pituitary TSH secretion, in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, Hashimoto’s thyroiditis, multinodular goiter and, as adjunctive therapy in the management of thyrotoxicosis and well-differentiated thyroid cancer (see INDICATIONS AND USAGE, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Pharmacokinetics
Absorption - Absorption of orally administered T4 from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of 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 soybean infant formula. Dietary fiber decreases bioavailability of T4. Absorption may also decrease with age. In addition, many drugs and foods affect T4 absorption (see PRECAUTIONS, Drug Interactions and Drug-Food Interactions).

Distribution - Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroid-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both T4 and TBA 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 Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only free hormone is biologically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins (see PRECAUTIONS, Drug Interactions and Drug-Laboratory Test Interactions). Thyroid hormones do not readily cross the placental barrier (see PRECAUTIONS, Pregnancy).

Metabolism - T4 is slowly eliminated (see Table 1). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty percent of circulating 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 (rT3). T4 and T4 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

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

INDICATIONS AND USAGE
Levothyroxine sodium is used for the following indications:

Hypothyroidism - As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyrotoxicosis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total congenital absence of the thyroid gland, or from the effects of surgery, radiation, or drugs, with or without the presence of goiter. Pituitary TSH Suppression - In the treatment or prevention of various types of euthyroid goiters (see WARNINGS and PRECAUTIONS), including thyroid nodules (see WARNINGS and PRECAUTIONS), subacute or chronic lymphocytic thyroiditis (Hashimoto’s thyroiditis), multinodular goiter (see WARNINGS and PRECAUTIONS) and, as an advance of surgery of thyroid disease, T4 therapy in the management of thyrotoxic- dependent well-differentiated thyroid cancer.

PRECAUTIONS
Levothyroxine is contraindicated in patients with untreated subclinical (suppressed serum TSH level with normal T4 and T3 levels) or overt thyrotoxicosis of any etiology and in patients with acute myocardial infarction. Levothyroxine is contraindicated in patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing glucocorticoid antagonism (see PRECAUTIONS). TIROSINT is contraindicated in patients with hypersensitivity to any of the inactive ingredients in TIROSINT capsules (see DESCRIPTION, Inactive Ingredients).

TIROSINT is also contraindicated for anyone who may be unable to swallow a capsule (e.g., infants, small children).

WARNINGS

Levothyroxine should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

In patients with diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine sodium therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitating overt thyrotoxicosis (see CONTRAINDICATIONS). If the serum TSH level is not suppressed, TIROSINT should be used with caution in conjunction with careful monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential of associated adverse cardiac events and symptoms of hyperthyroidism.

Drug Interactions

Effects on bone mineral density - In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and 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.

Patients with underlying cardiovascular disease - Exercise caution when administering levothyroxine to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease and it should be noted that unlike levothyroxine sodium tablets, TIROSINT capsules cannot be cut in half (see WARNINGS, PRECAUTIONS, Drug Interactions and DOSAGE AND ADMINISTRATION). If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Patients with nontoxic diffuse goiter or nodular thyroid disease - Exercise caution when administering levothyroxine to patients with nontoxic diffuse goiter or nodular thyroid disease in order to prevent precipitation of thyrotoxicosis (see WARNINGS). If the serum TSH is already suppressed, levothyroxine sodium should not be administered (see CONTRAINDICATIONS).

Associated endocrine disorders

Hypothalamic-pituitary hormone deficiencies - In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated (see PRECAUTIONS, Autoimmune polyglandular syndromes for adrenal insufficiency).

Autoimmune polyglandular syndromes - Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with levothyroxine sodium. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with levothyroxine (see PRECAUTIONS, Drug Interactions).

Other associated medical conditions

Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, with cardiovascular anomalies (pulmonary stenosis, atrial septal defect, and ventricular septal defect) being the most common association.

Table 1: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Ratio in Thyroglobulin</th>
<th>Biologic Potency</th>
<th>( t_1/2 ) (days)</th>
<th>Protein Binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levothyroxine (T4)</td>
<td>10 - 20</td>
<td>1</td>
<td>6 - 7</td>
<td>99.9%</td>
</tr>
<tr>
<td>L-thyroxine (T3)</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>99.5</td>
</tr>
</tbody>
</table>

3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism.

1 Includes TBG, TBPA, and TBA.
The recommended frequency of monitoring of TSH and total or free T4 in children is as follows: at 2 and
the child is not receiving adequate therapy. Careful inquiry should then be made regarding compliance,
the serum TSH to decrease below 20 mU/L within 4 weeks should alert the physician to the possibility that
increase into the upper half of the normal range within 2 weeks of initiation of TIROSINT therapy and/or of

**General Laboratory Tests**

**Pediatrics**

- Obtain TSH and T4 levels, and a physical examination, if indicated, be performed 4 weeks after the initiation of treatment; every 1-2 months during the first year of life; every 2-3 months
- May be used to monitor therapy. Frequency of monitoring during levothyroxine dose titration
- May not be comprehensive due to the introduction

**Laboratory Tests**

**Drugs that may increase TSH and T4 levels**

**Drugs that may decrease TSH and T4 levels**

**Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism**

**Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism**

**Drugs that may alter protein-binding site displacement**

**Drugs that may increase hepatic metabolism, which may result in hypothyroidism**

**Drugs that may decrease T4 absorption, which may result in hypothyroidism**

**Drugs that may cause thyroid hormone displacement**

**Drugs that may decrease T3 and T4 serum transport - but FT4 concentration remains normal, and therefore, the patient remains euthyroid**

**Drugs that may alter T4 and T3 metabolism**

**Drugs that may decrease TSH secretion - the reduction is not sustained; therefore, hypothyroidism does not occur**

**Dopamine**

**Acamprosate**

**Glucocorticoids**

**Octreotide**

**Table 2: Drug-Thyroidal Axis Interactions**

**Drugs that may decrease TSH secretion - the reduction is not sustained; therefore, hypothyroidism does not occur**
Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood of athymic fetuses being approximately one-third maternal levels. Transfer of thyroid hormones from the mother to the fetus, however, may not be adequate to prevent in utero hypothyroidism.

Nursing Mothers - Although thyroid hormones are excreted only minimally in human milk, caution should be exercised when TROSINT is administered to a nursing woman. However, adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

Pediatric Use

TROSINT is contraindicated for infants, small children or any child who may be unable to swallow a capsule.

Oral anticoagulants: Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be necessary in patients receiving levothyroxine. Serum prothrombin times should be monitored regularly, especially during the first 3 months of therapy.

Digitalis Gliclazides: Levothyroxine increases the plasma concentrations of gliclazides. Levothyroxine should be given at least 2 hours before or 4 hours after gliclazide.

Drug-Drug Interactions: Consumption of too much calcium or too much iron may reduce the absorption of levothyroxine. Some individuals may require higher doses in the presence of calcium supplements.

Drug-Laboratory Test Interactions: Changes in TSH concentrations have been noted in persons with thyrotoxicosis. Serial measurements of TSH and T4 may be necessary to monitor the response to treatment. The serum TSH levels may initially be suppressed, even if the serum T4 level is normal. If the patient has signs of hyperthyroidism, treatment should be withheld until the serum TSH level returns to normal.

Carcinogenesis, Mutagenesis, and Impairment of Fertility - Animal studies have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility. TROSINT should be given to pregnant women only if clearly needed.

OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism, and are treated with the same measures as are used for other hyperthyroid conditions. These measures include administration of anti-thyroid drugs, iodides, or beta-blocking agents. In rare instances of large overdosage, total thyroidectomy may be necessary. Cblorrhoids, shock, coma, and death have been reported. Severe depression of serum protein binding has been observed in patients receiving large doses. Seizures may occur in patients receiving large doses of levothyroxine. Symptoms may not necessarily be evident or may appear several days after ingestion of levothyroxine.

Acute Massive Overdose - This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. If not contraindicated (e.g., by seizures, coma, or loss of the gag reflex), the stomach should be emptied by emesis or gastric lavage to decrease gastrointestinal absorption. Activated charcoal or cholestyramine may also be used to decrease absorption.

Thyrotoxicosis - The signs and symptoms of thyrotoxicosis are those of hyperthyroidism, and are treated with the same measures as are used for other hyperthyroid conditions.
Central and peripheral increased sympathetic activity may be treated by administering α-receptor antagonists, e.g., propranolol, provided there are no medical contraindications to their use. Provide respiratory support as needed; control congestive heart failure and arrhythmia; control fever, hyperglycemia, and fluid loss as necessary. Large doses of antihistoid drugs (e.g., mebaral or procyclidine) followed in one to two hours by large doses of insulin may be given to inhibit synthesis and release of thyroid hormones. Glucocorticoids may be given to inhibit the conversion of T3 to T4. Plasma, gammapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy. Because T3 is highly protein bound, very little drug will be removed by dialysis.

**DOSAGE AND ADMINISTRATION**

**General Principles**

The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state. The goal of suppressive therapy is to inhibit growth and/or function of abnormal thyroid tissue. The dose of TSH that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see WARNINGS and PRECAUTIONS).

Hence, the following recommendations serve only as dosing guidelines. Dosage must be individualized and adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters (see PRECAUTIONS, Laboratory Tests).

TIROSINT® is administered as a single daily dose, preferably once-half to one-hour before breakfast. TIROSINT® should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (see PRECAUTIONS, Drug Interactions). TIROSINT® capsules cannot be cut or crushed. For children: the peak therapeutic effect at a given dose of levothyroxine sodium may not be attained for 4-6 weeks. Caution should be exercised when administering TIROSINT® to patients with underlying cardiovascular disease, to the elderly, and to those with comitant adrenal insufficiency (see PRECAUTIONS).

**Specific Patient Populations**

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

Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have not been recently treated for hypothyroidism or who have been hypothyroid for only a short time (such as a few months). The average full replacement dose of levothyroxine sodium is approximately 1.7 mcg/kg/day (age.100-125 mcg/day for a 70 kg adult). Older patients may require less than 1 mcg/kg/day. Levothyroxine sodium doses greater than 200 mcg/day are seldom required. An inadequate response to daily doses ≥ 300 mcg/day is rare and may indicate poor compliance, malabsorption, and/or drug interactions.

For most patients older than 50 years or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of 25-50 mcg/day of levothyroxine sodium is recommended, with gradual increments in doses at 4-8 week intervals, as needed. The recommended starting dose of levothyroxine sodium in elderly patients with cardiac disease is 12.5-25 mcg/day, with gradual dose increments at 4-6 week intervals. The levothyroxine sodium dose is generally adjusted in 12.5-25 mcg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized. Unlike levothyroxine sodium tablets, TIROSINT® capsules cannot be cut in half. In patients with severe hypothyroidism, the recommended initial levothyroxine sodium dose is 12.5-25 mcg/day with increases of 25 mcg/day every 2-4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized.

In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the levothyroxine sodium dose should be titrated until the patient is clinically euthyroid and the serum free-T3 level is restored to the upper half of the normal range. Pediatric Dosage - Congenital or Acquired Hypothyroidism (see PRECAUTIONS, Laboratory Tests).

**General Principles**

In general, levothyroxine therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development. Underdosing and overtreatment should be avoided (see PRECAUTIONS, Pediatric Use). TIROSINT® may be administered to infants and children, but only if they are able to swallow an intact capsule. Unlike levothyroxine sodium tablets, TIROSINT® capsules cannot be crushed and suspended in a small amount of water, nor can they be dissolved by placing in water prior to administration (see CONTRAINDICATIONS).

**Newborns**

TIROSINT® is not recommended for the treatment of newborns as they may be unable to swallow a capsule. Infants and Children

Levothyroxine therapy is usually initiated at full replacement doses, with the recommended dose per body weight decreasing with age (see Table 3). However, in children with chronic or severe hypothyroidism, an initial dose of 25 mcg/kg/day of levothyroxine sodium is recommended with increments of 25 mcg every 2-4 weeks until the desired effect is achieved. Hy poactivity 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 onefourth the full-recommended replacement dose until the full-recommended replacement dose is reached.

**Subclinical Hypothyroidism**

If this condition is treated, a lower levothyroxine sodium dose (e.g., 1 mcg/kg/day) than that used for full replacement may be adequate to normalize the serum TSH level. Patients who are not treated should be monitored yearly for changes in clinical status and thyroid laboratory parameters.

**TSH Suppression in Well-Differentiated Thyroid Cancer and Thyroid Nodules:** The target level for TSH suppression in these conditions has not been established with controlled studies. In addition, the efficacy of TSH suppression for benign nodular disease is controversial. Therefore, the dose of TIROSINT® used for TSH suppression should be individualized based on the specific disease and the patient being treated.

In the treatment of well-differentiated papillary (and follicular) thyroid cancer, levothyroxine is used as an adjutant to surgery and radioactive iodine therapy. Generally, TSH is suppressed to <0.1 mIU/L, and this usually requires a levothyroxine sodium dose of greater than 2 mcg/kg/day. However, in patients with high-risk tumors, the target level for TSH suppression may be <0.01 mIU/L.

In the treatment of benign nodules and non-toxic multinodular goiter, TSH is generally suppressed to a higher target (e.g., 0.1 to either 0.5 or 1.0 mIU/L) than that used for the treatment of thyroid cancer. Levothyroxine sodium is contraindicated if the serum TSH is already suppressed due to the risk of precipitating overt thyrotoxicosis (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

**Myxedema Coma -** Myxedema coma is a life-threatening emergency characterized by poor circulation and hypotension, and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral thyroid hormone drug products are not recommended to treat this condition. Thyroid hormone products formulated for intravenous administration should be administered.

**HOW SUPPLIED**

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

1. Boxes of 28 capsules, consisting of 4 blisters with 7 capsules each.

The dosages strength on each box is clearly identified in several locations, and is associated with a distinct color (see Table below). 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. Please 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).

<table>
<thead>
<tr>
<th>Strength (mcg)</th>
<th>Color*</th>
<th>NDC</th>
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</thead>
<tbody>
<tr>
<td>13</td>
<td>green</td>
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</tr>
<tr>
<td>25</td>
<td>orange</td>
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<td>150</td>
<td>blue</td>
<td>24070-499-84</td>
</tr>
</tbody>
</table>

* On-box and blister packing, not in individual capsules.

**Storage Conditions**

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 light and moisture.

**Manufactured for Akrimax Pharmaceuticals, LLC by:**

IBSA Institut Bioclinique SA,
6903 Lugano, Switzerland

**Marketed & Distributed by:**

Akrimax Pharmaceuticals, LLC
Cranford, NJ 07016 USA

For further product information and current package insert, please call our Customer Service number toll free at: 888.383.1733.