CLINICAL UPDATE

Brand Name	Tirosint®-Sol
Generic Name	levothyroxine sodium
Drug Manufacturer	IBSA Pharma Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New strength

FDA APPROVAL DATE

January 13, 2021

LAUNCH DATE

July 19, 2021

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

New Drug Application (NDA): 206977

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Tirosint®-Sol is L-thyroxine (T4) indicated for:

- Hypothyroidism - As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.
- 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.

MECHANISMS 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.

DOSAGE FORM(S) AND STRENGTH(S)

Oral solution: 13, 25, 37.5, 44, 50, 62.5, 75, 88, 100, 112, 125, 137, 150, 175, 200 mcg/mL.

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Strength (mcg/mL)	Color[a]	Box NDC (30 Unit-Dose Ampules)	Pouch NDC (5 Unit-Dose Ampules)
13	Green	25121-101-30	25121-101-05
25	Orange	25121-102-30	25121-102-05
50	White	25121-103-30	25121-103-05
75	Purple	25121-104-30	25121-104-05
88	Olive	25121-105-30	25121-105-05
100	Yellow	25121-106-30	25121-106-05
112	Rose	25121-107-30	25121-107-05
125	Brown	25121-108-30	25121-108-05
137	Turquoise	25121-109-30	25121-109-05
150	Blue	25121-110-30	25121-110-05
175	Lilac	25121-111-30	25121-111-05
200	Pink	25121-112-30	25121-112-05

[a] Shown on box, pouch and ampule.

DOSE & ADMINISTRATION

- Administer once daily, on an empty stomach, one-half to one hour before breakfast.
- Administer at least 4 hours before or after drugs that are known to interfere with absorption.
- Evaluate the need for dose adjustments when regularly administering within an hour of certain foods that may affect Tirosint®-Sol absorption.
- To administer Tirosint®-Sol in water, squeeze the contents of one single unit-dose ampule into a glass or cup containing water.
- To administer Tirosint®-Sol directly, either squeeze it into the mouth OR onto a spoon and immediately consume.
- Starting dose depends on a variety of factors, including age, body weight, cardiovascular status, concomitant medical conditions (including 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.
- Adequacy of therapy determined with periodic monitoring of TSH and/or T4 as well as clinical status.

EFFICACY

Three bioequivalence studies were conducted and included phase one bioequivalence study between new levothyroxine solution oral solution (LSOS) and the reference drug list. However, there were no studies conducted for clinical efficacy trials.

CRO – IBSA Study #s (Module)	Route	Study design	Subject Enrolled/Evaluated	Conclusion
130284 - 13CDN/T406 (Module 5.3.1.2.2, Study Report Body)	Oral	Single center, randomized, single dose, open-label, 3-way crossover comparative bioavailability study	36 / -	Bioequivalence assessment invalidated by inappropriate dosing caused by improper dispensation from the LSOS ampules
140143 - 14CDN/T405 (Module 5.3.1.2.3, Study Report Body)	Oral	Pilot, single center, randomized, single dose, open-label, 3-way crossover comparative bioavailability study	9 / 8	600 mcg total doses of LSOS and Tirosint capsules were bioequivalent.
140161 - 14CDN/T403 (Module 5.3.1.2.1, Study Report Body)	Oral	Single center, randomized, single-dose, open-label, 3-way crossover comparative bioavailability study	36 / 34 36 / 32	600 mcg total doses of LSOS and Tirosint capsules were bioequivalent. 600 mcg total doses of LSOS administered either following dilution in water or introduction directly into the oral cavity were bioequivalent.

Source: Applicant Table 2.5-1, Clinical Overview