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<td><strong>Submit Date(s)</strong></td>
<td>February 26, 2016</td>
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<td><strong>Received Date(s)</strong></td>
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<td><strong>Reviewer Name(s)</strong></td>
<td>John Sharretts, M.D.</td>
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<td><strong>Review Completion Date</strong></td>
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<td><strong>Established Name</strong></td>
<td>Levothyroxine sodium</td>
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<tr>
<td><strong>(Proposed) Trade Name</strong></td>
<td>Tirosint-SOL</td>
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<td><strong>Therapeutic Class</strong></td>
<td>Thyroid hormone</td>
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<tr>
<td><strong>Applicant</strong></td>
<td>Institut Biochimique SA (IBSA)</td>
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<td><strong>Formulation(s)</strong></td>
<td>Oral solution</td>
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<td>13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 mcg/mL</td>
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<td><strong>Indication(s)</strong></td>
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*Template Version: March 6, 2009*
# Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT ................................. 7
   1.1 Recommendation on Regulatory Action ........................................... 7
   1.2 Risk Benefit Assessment ................................................................. 7
   1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ... 7
   1.4 Recommendations for Postmarket Requirements and Commitments .......... 7

2 INTRODUCTION AND REGULATORY BACKGROUND ........................................ 8
   2.1 Product Information ........................................................................... 9
   2.2 Tables of Currently Available Treatments for Proposed Indications .......... 10
   2.3 Availability of Proposed Active Ingredient in the United States ................. 11
   2.4 Important Safety Issues with Consideration to Related Drugs .................. 11
   2.5 Summary of Presubmission Regulatory Activity Related to Submission ....... 12
   2.6 Other Relevant Background Information ............................................ 13

3 ETHICS AND GOOD CLINICAL PRACTICES ....................................................... 13
   3.1 Submission Quality and Integrity ....................................................... 13
   3.2 Compliance with Good Clinical Practices ......................................... 13
   3.3 Financial Disclosures ........................................................................ 13

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW
   DISCIPLINES .................................................................................................... 13
   4.1 Office of Pharmaceutical Quality ....................................................... 13
   4.3 Preclinical Pharmacology/Toxicology ............................................... 13
   4.4 Clinical Pharmacology ....................................................................... 13
       4.4.1 Mechanism of Action ................................................................. 14
       4.4.2 Pharmacodynamics ................................................................. 14
       4.4.3 Pharmacokinetics ................................................................. 14

5 SOURCES OF CLINICAL DATA ........................................................................... 16
   5.1 Tables of Studies/Clinical Trials ....................................................... 16
   5.2 Review Strategy ............................................................................... 16
   5.3 Discussion of Individual Studies/Clinical Trials .................................... 16

6 REVIEW OF EFFICACY ................................................................................... 26
   Efficacy Summary ..................................................................................... 26
   6.1 Indication .......................................................................................... 27
       6.1.1 Methods .................................................................................... 27
       6.1.2 Demographics .......................................................................... 27
       6.1.3 Subject Disposition ................................................................. 30
       6.1.4 Analysis of Primary Endpoint(s) ............................................... 32
       6.1.5 Analysis of Secondary Endpoint(s) ............................................ 34
       6.1.6 Other Endpoints ...................................................................... 34

Reference ID: 4023308
6.1.7 Subpopulations ........................................................................................................ 34
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations .......... 34
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects ......................... 35
6.1.10 Additional Efficacy Issues/Analyses ................................................................. 35

7 REVIEW OF SAFETY ................................................................................................. 35

Safety Summary ........................................................................................................... 35
7.1 Methods .................................................................................................................. 35
7.1.1 Studies/Clinical Trials Used to Evaluate Safety .................................................. 35
7.1.2 Categorization of Adverse Events ...................................................................... 36
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence ................................................................................................................................. 36
7.2 Adequacy of Safety Assessments ........................................................................ 37
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations ................................................................................................................................. 37
7.2.2 Explorations for Dose Response ........................................................................ 37
7.2.3 Special Animal and/or In Vitro Testing ............................................................... 37
7.2.4 Routine Clinical Testing ...................................................................................... 37
7.2.5 Metabolic, Clearance, and Interaction Workup .................................................. 38
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ......... 38
7.3 Major Safety Results ............................................................................................ 38
7.3.1 Deaths ................................................................................................................ 38
7.3.2 Nonfatal Serious Adverse Events ....................................................................... 38
7.3.3 Dropouts and/or Discontinuations ..................................................................... 38
7.3.4 Significant Adverse Events ............................................................................... 38
7.3.5 Submission Specific Primary Safety Concerns .................................................... 39
7.4 Supportive Safety Results .................................................................................... 39
7.4.1 Common Adverse Events .................................................................................. 39
7.4.2 Laboratory Findings .......................................................................................... 39
7.4.3 Vital Signs ......................................................................................................... 41
7.4.4 Electrocardiograms (ECGs) .............................................................................. 41
7.4.5 Special Safety Studies/Clinical Trials ................................................................. 41
7.4.6 Immunogenicity ................................................................................................ 41
7.5 Other Safety Explorations ................................................................................... 42
7.5.1 Dose Dependency for Adverse Events ............................................................... 42
7.5.2 Time Dependency for Adverse Events .............................................................. 42
7.5.3 Drug-Demographic Interactions ....................................................................... 42
7.5.4 Drug-Disease Interactions ............................................................................... 42
7.5.5 Drug-Drug Interactions ................................................................................... 42
7.6 Additional Safety Evaluations ............................................................................. 42
7.6.1 Human Carcinogenicity .................................................................................... 42
7.6.2 Human Reproduction and Pregnancy Data ....................................................... 42
7.6.3 Pediatrics and Assessment of Effects on Growth .............................................. 42
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound ............................. 42
7.7 Additional Submissions / Safety Issues ................................................................. 43

8 POSTMARKET EXPERIENCE ........................................................................................................ 43

9 APPENDICES ........................................................................................................................................ 44

  9.1 Literature Review/References ........................................................................................................ 44
  9.2 Labeling Recommendations ........................................................................................................ 45
  9.3 Advisory Committee Meeting .................................................................................................... 45
Clinical Review
John Sharretts, M.D.
NDA 206977
Tirosint-SOL (levothyroxine sodium oral solution)

Table of Tables

Table 1: Approved Oral Thyroid Hormone Products Approved for Treatment of Hypothyroidism and TSH Suppression for Differentiated Thyroid Cancer ..... 10
Table 2: Studies by the Applicant with Levothyroxine Sodium Oral Solution............... 16
Table 3: Test Products (Study 130284 – 13CDN/T406).................................................. 18
Table 4: Test Products (Study 140143 – 14CDN/T405).................................................. 20
Table 5: Test Products (Study 140161 – 14CDN/T403).................................................. 24
Table 6: Demographics and Baseline Characteristics (Safety Population, Study 130284 – 13CDN/T406))........................................................................................................ 28
Table 7: Demographics and Baseline Characteristics (Safety Population, Study 140143 – 14CDN/T405)........................................................................................................ 29
Table 8: Demographics and Baseline Characteristics (Safety Population, Study 140161 – 14CDN/T403)........................................................................................................ 30
Table 9: Ratios and 90% Geometric Confidence Intervals for AUC0-48 and Cmax for Baseline-Corrected Levothyroxine (Study 130284 – 13CDN/T406).................. 32
Table 10: Ratios and 90% Geometric Confidence Intervals for AUC0-48 and Cmax for Baseline-Corrected Levothyroxine (Study 140143 – 14CDN/T405).................. 33
Table 11: Ratios and 90% Geometric Confidence Intervals for AUC0-48 and Cmax for Baseline-Corrected Levothyroxine (Study 140161 – 14CDN/T403).................. 34
Table 12: Subject Exposure by Treatment (by Study and Overall)................................. 37
Table of Figures

No table of figures entries found.
1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend in favor of approval of the application.

1.2 Risk Benefit Assessment

Benefit
The Applicant is seeking marketing authorization through a 505(b)(2) New Drug Application. The Applicant completed one pivotal bioavailability study (Study 140161 – 14 CDN/T403) to establish bioequivalence between the new levothyroxine sodium oral solution formulation (Tirosint-SOL) and the reference product, Tirosint 150 mcg capsules. The Applicant did not conduct any new clinical efficacy studies to support the application. In Study 140161, the test product (levothyroxine sodium oral solution administered with water) met the pre-specified criteria for demonstration of bioequivalence with the reference product (Tirosint capsules). Refer to the clinical pharmacology review for full analysis of the results of the pivotal study.

The Applicant may rely on FDA findings of safety and efficacy for the reference listed drugs, Tirosint (levothyroxine sodium capsules) NDA 021924 (for doses between 13 mcg and 150 mcg), and Synthroid (levothyroxine sodium) tablets NDA 021402 (for the 175 mcg and 200 mcg doses and for pediatric patients under six years old).

Risk
The risk-benefit profile of the reference listed drugs supports approval. The Applicant submitted pooled safety data from three biopharmaceutical studies in support of the application. The Applicant reported no deaths or non-fatal serious adverse events in any study. Treatment-emergent adverse events, clinical laboratory results, vital signs and ECG findings did not identify any new safety concerns with the new formulation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None
2 Introduction and Regulatory Background

Hypothyroidism is a chronic disorder caused by decreased secretion of the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃) by the thyroid gland. The etiology can be due to disease or absence of the thyroid gland (primary), impaired or absent secretion of thyrotropin (TSH) by the pituitary gland (secondary), or impaired or absent secretion of thyrotropin-releasing hormone (TRH) by the hypothalamus (tertiary). Secondary and tertiary hypothyroidism may be isolated or associated with other pituitary hormone deficiencies.¹

The most common cause of hypothyroidism worldwide is dietary iodine deficiency. In iodine-sufficient populations, the most common cause is autoimmune thyroid disease. Other causes of primary hypothyroidism include surgical resection or radioiodine ablation of the thyroid gland for treatment of hyperthyroidism, thyroid cancer, or benign nodular thyroid disease, congenital absence of dysfunction of the thyroid gland, and external beam radiation for non-thyroid malignancy. Causes of secondary or tertiary hypothyroidism include tumors, trauma, infiltrative disease, radiation, and congenital anomalies.

Common clinical manifestations of hypothyroidism include fatigue, weight gain, dry skin, cold intolerance, constipation, and non-pitting edema. Congenital hypothyroidism causes growth failure and cognitive dysfunction in children. Consequences of severe hypothyroidism include hyperlipidemia, hyperprolactinemia, and hyponatremia.¹

The prevalence of hypothyroidism ranges from 0.2% to 4.6%.²³⁴ Hypothyroidism is more common in females than males, and prevalence increases with age. Treatment of hypothyroidism consists of replacement of thyroid hormone, most commonly levothyroxine (T₄), although some practitioners favor partial substitution of T₄ with liothyronine (T₃) in selected patients, despite a lack of evidence supporting additional clinical benefit with this approach.³

Clinical Review
John Sharretts, M.D.
NDA 206977
Tirosint-SOL (levothyroxine sodium oral solution)

Thyrotropin-dependent differentiated thyroid cancer (DTC) encompasses papillary carcinoma and follicular carcinoma of the thyroid. The annual incidence of DTC ranges from 0.5 to 10 cases per 100,000 per year, and is more common in iodine deficient populations. The primary treatments for DTC are surgical resection of the thyroid gland and local metastases to cervical lymph nodes, combined with radiiodine ablation of remnant thyroid tissue in some cases. Suppression of pituitary TSH with thyroid hormone is a common adjunctive treatment in higher-risk tumors and distant metastatic disease.8

2.1 Product Information

Tirosint-SOL (levothyroxine sodium oral solution) is a liquid formulation of levothyroxine dissolved in glycerol produced in 12 strengths containing 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, or 200 mcg of levothyroxine. Each unit dose is packaged in a white, non-transparent, low-density polyethylene ampule with a nominal volume of mL. The Applicant, IBSA, submitted a 505(b)(2) application relying on previous FDA findings of safety and efficacy for the listed drugs Tirosint (levothyroxine sodium) capsules (NDA 021924) for dose strengths from 13 to 150 mcg and Synthroid (levothyroxine sodium) tablets (NDA 021402) for the 175 and 200 mcg dose strengths as well as for pediatric use in patients under 6 years of age. Tirosint capsules were originally approved under a 505(b)(2) application also relying on previous findings of safety and efficacy for the reference listed drug, Synthroid tablets (NDA 021402).

The proposed indications for Tirosint-SOL are:

- **Hypothyroidism:** as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism.
- **Pituitary Thyrotropin Stimulating Hormone (TSH) Suppression:** as an adjunct to surgery and radiiodine therapy in the management of thyrotropin-dependent, well-differentiated thyroid cancer.

The current formulation of levothyroxine sodium oral solution (Tirosint-SOL) is not approved or marketed in any other countries. The Applicant currently markets a similar product, levothyroxine sodium oral solution containing, approved for marketing in Italy in February 2012 at strengths of 25, 50, 75, and 100 mcg/mL.

---

8 Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016; 26: 1-133.
The Applicant is relying on one pivotal comparative bioavailability study (Study 140161 – 14CDN/T403) to establish bioequivalence of the new oral solution formulation to Tirosint 150 mcg capsule and provide a scientific bridge between the oral solution and the clinical safety and efficacy data for the listed drug, Tirosint capsules. The Applicant requested a waiver from a dosage-form proportionality study.

2.2 Tables of Currently Available Treatments for Proposed Indications

Five manufacturers currently market branded, approved formulations of levothyroxine sodium tablets in the United States, and IBSA markets an approved formulation of levothyroxine capsules. One manufacturer currently markets an approved generic formulation of levothyroxine tablets. Three branded formulations of levothyroxine sodium tablets are approved but not currently marketed. All levothyroxine products are approved for treatment of hypothyroidism and TSH suppression for differentiated thyroid cancer. One manufacturer currently markets a branded formulation of liothyronine sodium (T₃) approved for treatment of hypothyroidism. Table 1 summarizes oral thyroid hormone products.

Table 1: Approved Oral Thyroid Hormone Products Approved for Treatment of Hypothyroidism and TSH Suppression for Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Application number</th>
<th>Manufacturer</th>
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<tr>
<td><strong>Approved Levothyroxine Sodium Products</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Levo-T</td>
<td>NDA 021342</td>
<td>Alara</td>
<td>Tablet</td>
</tr>
<tr>
<td>Levoxyl</td>
<td>NDA 021301</td>
<td>King</td>
<td>Tablet</td>
</tr>
<tr>
<td>Synthroid</td>
<td>NDA 021402</td>
<td>Abbvie</td>
<td>Tablet</td>
</tr>
<tr>
<td>Tirosint</td>
<td>NDA 021924</td>
<td>IBSA</td>
<td>Capsule</td>
</tr>
<tr>
<td>NDA 022121</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unithroid</td>
<td>NDA 021210</td>
<td>Jerome Stevens</td>
<td>Tablet</td>
</tr>
<tr>
<td>Levothyroxine sodium</td>
<td>ANDA 076187</td>
<td>Mylan</td>
<td>Tablet</td>
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<table>
<thead>
<tr>
<th><strong>Approved Levothyroxine Sodium Products Not Currently Marketed</strong></th>
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<tr>
<td>Levolet</td>
<td>NDA 021137</td>
</tr>
<tr>
<td>Thyro-Tabs (Levothroid)</td>
<td>NDA 021116</td>
</tr>
<tr>
<td>Novothyrox</td>
<td>NDA 021292</td>
</tr>
</tbody>
</table>

| **Approved Liothyronine Products**               |                  |                     |             |
| Cytomel*                     | NDA 010379      | Pfizer              | Tablet      |

*Cytomel is not approved for treatment of thyroid cancer
2.3 Availability of Proposed Active Ingredient in the United States

Several manufacturers market approved oral formulations of levothyroxine in the United States as described in Section 2.2. Additionally Levothyroxine Sodium for Injection is approved for treatment of myxedema coma. Three manufacturers currently market formulations of levothyroxine for injection: Fresenius Kabi (NDA 202231), Par Pharmaceuticals (ANDA 205366), and Fera Pharmaceuticals LLC (ANDA 206163).

2.4 Important Safety Issues with Consideration to Related Drugs

Over- or Under-Replacement with Thyroid Hormone
Thyroid hormones have a narrow therapeutic index. Over- or under-treatment with levothyroxine 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.

Cardiac Adverse Reactions
Overtreatment with thyroid hormone may cause increase in heart rate, cardiac wall thickness and cardiac contractility, and may precipitate angina or arrhythmias, particularly in elderly patients and patients with underlying cardiovascular disease.

Acute Adrenal Crisis in Patients with Concomitant Adrenal Insufficiency
Thyroid hormones increase metabolic clearance of glucocorticoids. Initiation of thyroid hormone therapy prior to glucocorticoid therapy may precipitate an acute adrenal crisis.

Worsening of Diabetic Control
Initiation of thyroid hormone therapy may worsen diabetic control and cause hyperglycemia in patients with diabetes mellitus.

Decreased Bone Mineral Density Associated with Thyroid Hormone Over-Replacement
Over-replacement with thyroid hormones may cause increased bone resorption and decreased bone mineral density, particularly in post-menopausal women.

Myxedema Coma
Myxedema coma may result in unpredictable absorption of levothyroxine from the gastrointestinal tract. Use of oral thyroid hormone drug products is not recommended in patients with myxedema coma. Health care practitioners should use thyroid hormone products formulated for intravenous administration to treat myxedema coma.

Common Adverse Reactions
Other adverse reactions associated with levothyroxine therapy are primarily those due to therapeutic overdose, including (but not exclusive to) increased appetite, weight loss, heat intolerance, excessive sweating, headache, hyperactivity, nervousness, anxiety,
Clinical Review  
John Sharretts, M.D.  
NDA 206977  
Tirosint-SOL (levothyroxine sodium oral solution)

irritability, insomnia, tremors, muscle weakness, palpitations, tachycardia, increased pulse, dyspnea, diarrhea, hair loss, flushing, and menstrual irregularities.

Adverse Reactions in Children  
Pseudotumor cerebri and slipped capital femora epiphysis are associated with initiation of levothyroxine therapy in children. Over-replacement in children may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Hypersensitivity Reactions  
Patients treated with thyroid hormone products have experienced hypersensitivity reactions to inactive ingredients, including urticaria, pruritus, skin rash, flushing, angioedema, gastrointestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea), fever, arthralgia, serum sickness and wheezing.

2.5 Summary of Presubmission Regulatory Activity Related to Submission  
The Applicant submitted Investigational New Drug (IND) application 115023 in September 2012 for an oral liquid formulation containing levothyroxine sodium. The IND included a proposed Phase 1 bioequivalence study between the new levothyroxine sodium oral solution product and the reference listed drug, Tirosint capsules. The Applicant subsequently completed the proposed study as well as a 3-way crossover study of the oral solution diluted in water in fasting and fed subjects and dispensed directly into the oral cavity without water in fasting subjects.

At a pre-NDA meeting with the Division of Metabolism and Endocrinology Products in June 2013, the Division raised concerns with the formulation with regards to the presence of glycerol in the entire pediatric population. The Division of Medication Error Prevention and Analysis (DMEPA) raised concern about the possibility for medication errors due to the similarity of the ampules among the different dosage strengths as well as the similarity of the ampules to other ampules for unrelated inhalation and ophthalmic products. Subsequent to the meeting, the Applicant proposed to reformulate the oral solution. The Office of New Drug Quality Assessment reviewer found the proposed changes acceptable. The Applicant also submitted a revised packaging proposal to DMEPA. The DMEPA reviewer concluded that the proposed label, labeling, and packaging were acceptable from a medication error perspective.

The Applicant submitted an initial Pediatric Study Plan (iPSP) in February 2014. The Pediatric Review Committee (PeRC) agreed to use data from the oral solution formulation and proposed the use of intravenous levothyroxine to replace oral levothyroxine as the comparator treatment in the pediatric trials. The Applicant submitted a revised iPSP in June 2014, and the Division agreed to the plan in July 2015.
2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The organization of the submission was appropriate. Datasets for the pivotal study were in reviewable electronic format.

3.2 Compliance with Good Clinical Practices

The Applicant attested that investigators conducted the primary clinical study under the provisions of the Declaration of Helsinki, and in accordance with the International Conference of Harmonisation (ICH) Consolidated Guideline on Good Clinical Practice (GCP) and all local regulatory requirements.

3.3 Financial Disclosures

The Sponsor submitted FDA form 3454 with the names and contact information for all participating investigators in the submitted studies. None of the clinical investigators had a financial interest requiring disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Office of Pharmaceutical Quality

Please refer to the review (Lead: Suong Tran). OPQ recommends approval.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the review by Dr. Parvaneh Espandiari, who recommends approval.

4.4 Clinical Pharmacology

Please refer to the review by Dr. Johnny Lau, who recommends approval.
4.4.1 Mechanism of Action

Thyroid hormones exert their physiologic actions through control of DNA transcription and protein synthesis. T₃ and 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.⁷

4.4.2 Pharmacodynamics

Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin (thyroid stimulating hormone, TSH), from the anterior pituitary. TSH, in turn, is the physiologic 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.

TSH, along with T₄ levels and other laboratory and clinical data, is primarily used for both the diagnosis of hypothyroidism and evaluation of levothyroxine therapy adequacy. There are drugs known to affect thyroid hormones and TSH levels by various mechanisms. Some drugs may cause a transient decrease in TSH secretion without hypothyroidism: dopamine (≥1 mcg per kg per min), glucocorticoids (hydrocortisone ≥100 mg per day or equivalent) and octreotide (> 100 mcg per day).

Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates, and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development.

4.4.3 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

⁷ Source: Adapted from Tirosint capsules package insert (PI) and proposed Tirosint-SOL PI
ileum. T<sub>4</sub> absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybeans. Dietary fiber decreases the bioavailability of T<sub>4</sub>. Absorption may also decrease with age. In addition, many drugs and foods affect T<sub>4</sub> absorption.

**Distribution**
Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T<sub>4</sub> partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T<sub>4</sub> compared to T<sub>3</sub>. 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. Thyroid hormones do not readily cross the placental barrier.

**Metabolism**
T<sub>4</sub> is slowly eliminated. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T<sub>3</sub> is derived from peripheral T<sub>4</sub> by monodeiodination. The liver is the major site of degradation for both T<sub>4</sub> and T<sub>3</sub>, with T<sub>4</sub> deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T<sub>4</sub> is deiodinated to yield equal amounts of T<sub>3</sub> and reverse T<sub>3</sub> (r T<sub>3</sub>). T<sub>3</sub> and r T<sub>3</sub> are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

**Elimination**
Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T<sub>4</sub> is eliminated in the stool. Urinary excretion of T<sub>4</sub> decreases with age. T<sub>4</sub> is 99.96% bound to protein (TBG, TBPA, and TBPA) and has a half-life of approximately 6-7 days. T<sub>3</sub> is 99.5% bound to proteins and has a half-life of less than two days.
5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Studies by the Applicant with Levothyroxine Sodium Oral Solution

<table>
<thead>
<tr>
<th>Study #</th>
<th>Route</th>
<th>Study design</th>
<th>Subject Enrolled/Evaluated</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>130284 - 13CDN/T406 (Module 5.3.1.2.2, Study Report Body)</td>
<td>Oral</td>
<td>Single center, randomized, single dose, open-label, 3-way crossover comparative bioavailability study</td>
<td>36 / -</td>
<td>Bioequivalence assessment invalidated by inappropriate dosing caused by improper dispensation from the LSOS ampules</td>
</tr>
<tr>
<td>140143 - 14CDN/T405 (Module 5.3.1.2.3, Study Report Body)</td>
<td>Oral</td>
<td>Pilot, single center, randomized, single dose, open-label, 3-way crossover comparative bioavailability study</td>
<td>9 / 8</td>
<td>600 mcg total doses of LSOS and Tirosint capsules were bioequivalent.</td>
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<tr>
<td>140161 - 14CDN/T403 (Module 5.3.1.2.1, Study Report Body)</td>
<td>Oral</td>
<td>Single center, randomized, single-dose, open-label, 3-way crossover comparative bioavailability study</td>
<td>36 / 34</td>
<td>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.</td>
</tr>
</tbody>
</table>

Source: Applicant Table 2.5-1, Clinical Overview

5.2 Review Strategy

The Applicant conducted three bioequivalence studies to support registration of the product. The Applicant did not conduct any clinical efficacy trials. Refer to the Clinical Pharmacology Review for details of the determination of bioequivalence. This review focuses on safety findings.

5.3 Discussion of Individual Studies/Clinical Trials

Study 130284 - 13CDN/T406 (Study 130284)

Title: Randomized, Open-Label, 3-Way Crossover Comparative Bioavailability Study of Levothyroxine Sodium Oral Solution (Test) Administered With and Without Water and Tirosint Capsules (Reference) Following a Single Oral Dose of 600 µg in Healthy Subjects Under Fasting Conditions

Reference ID: 4023308
Design:
Single center, randomized, single-dose, open-label, three-way crossover comparative bioavailability study

Objectives:
The primary objective was to compare the rate and extent of absorption of levothyroxine sodium oral solution 150 mcg unit-dose ampules administered with water (Test, Treatment A) versus Tirosint 150 mcg capsules (Reference, Treatment C) administered as a 600 mcg oral dose under fasting conditions.

The secondary objective was to compare the rate and extent of absorption of levothyroxine sodium oral solution 150 mcg unit-dose ampules administered without water (Test, Treatment B) versus levothyroxine sodium oral solution 150 mcg unit-dose ampules administered with water (Test, Treatment A), administered as a 600 mcg oral dose under fasting conditions.

Study Population:
Healthy adult subjects, 18 to 50 years
- Non-smoker or moderate smoker
- Body mass index (BMI) > 18.5 kg/m² and < 30.0 kg/m²

Number of Subjects: 36

Schedule:
Screening procedures included informed consent, inclusion and exclusion criteria, medical history, medication history, demographics, body measurements, vital signs, ECG, physical examination, and clinical laboratory tests (including drug screen and pregnancy test).

The study consisted of three test periods separated by 35-day washout periods. Investigators randomized subjects to one of three treatment sequences. During each test period, investigators confined subjects from at least 10 hours prior to drug administration until after the 48-hour blood collection in each study period. Investigators collected blood samples for each period at -0.500 hour, -0.250 hour and within five minutes (0 hour) prior to dosing, and at 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0, and 48.0 hours post-dose.

Test Products:
Refer to Table 3.
Clinical Review  
John Sharrett's, M.D.  
NDA 206977  
Tirosint-SOL (levothyroxine sodium oral solution)

**Table 3: Test Products (Study 130284 – 13CDN/T406)**

<table>
<thead>
<tr>
<th>Product</th>
<th>Tests</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment ID</td>
<td>A and B</td>
<td></td>
</tr>
<tr>
<td>Product Name</td>
<td>Levothyroxine sodium oral solution</td>
<td>Tirosint® (levothyroxine sodium)</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>IBSA Institut Biochimique SA, Switzerland</td>
<td>IBSA Institut Biochimique SA, Switzerland</td>
</tr>
<tr>
<td>Batch/Lot No.</td>
<td>130802</td>
<td>13006</td>
</tr>
<tr>
<td>Manufacture Date</td>
<td>August 2013</td>
<td>June 2013</td>
</tr>
<tr>
<td>Expiration Date</td>
<td></td>
<td>(01/04)</td>
</tr>
<tr>
<td>Strength</td>
<td>150 μg/mL</td>
<td>150 μg</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Single-dose ampule (1 mL)</td>
<td>Capsule</td>
</tr>
<tr>
<td>Potency</td>
<td>99.2%</td>
<td>98.2%</td>
</tr>
<tr>
<td>Dose Administered</td>
<td>4 x 150 μg</td>
<td>4 x 150 μg</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Source: Applicant Table 9.4.2-1, Clinical Study Report, Study 130284

**Safety Assessments:**
Adverse Events, Vital Signs, ECG, clinical laboratory

**Statistical Methods:**
Safety – descriptive statistics
Pharmacokinetics:
- Criteria for evaluation: $AUC_{0-48}, C_{max}$, and $T_{max}$
- Parametric ANOVA
- Geometric confidence intervals for each treatment comparison

**Changes in Study Conduct:**
Investigators discovered that the procedure used for emptying the unit-dose ampules was inappropriate, resulting in administration of an incomplete dose. The Investigators issued an abbreviated study report in lieu of a full clinical and statistical report.

**Study 140143 – 14CDN/T405 (Study 140143)**

**Title:** Pilot, Randomized, Open-Label, 3-Way Crossover Comparative Bioavailability Study of Levothyroxine Sodium Oral Solution (Test), Tirosint Capsules (Reference 1), and Tirosint Oral Solution (Reference 2), Following a Single Oral Dose of 600 μg in Healthy Subjects Under Fasting Conditions

**Design:**
Single center, randomized, single-dose, open-label, three-way crossover comparative bioavailability study
Objectives:
The objective of this study was to compare the rate and extent of absorption of levothyroxine sodium oral solution 150 mcg unit-dose ampules (Test) versus Tirosint 150 mcg capsules (Reference-1) and Tirosint oral solution 100 mcg unit-dose ampules (Reference-2), administered as a 600 mcg oral dose under fasting conditions.

The purpose of the study was to demonstrate preliminary evidence of bioequivalence of the test product to the reference products when subjects followed revised dosing instructions updated after the previous failed bioequivalence study (Study 130284 – 13CDN/T406).

Study Population:
Healthy adult subjects, 18 to 50 years

Key inclusion criteria
- Non-smoker or moderate smoker
- Body mass index (BMI) > 18.5 kg/m² and < 30.0 kg/m²
- Body weight ≥ 50 kg (males) and ≥ 45 kg (females)
- Acceptable non-hormonal contraception (females of childbearing potential)

Key exclusion criteria
- Clinically significant abnormal laboratory results
- Positive pregnancy test or currently breastfeeding
- ECG or vital sign abnormalities
- History of alcohol or drug abuse within one year or positive drug screen
- Use of contraindicated medications
- Plasma donation within seven days, blood donation (499 mL) within 30 days or blood loss (> 499 mL) within 56 days

Withdrawal and re-entry criteria
Investigators could withdraw subjects for various reasons, including adverse reactions, non-compliance, protocol deviations, unscheduled concomitant medications, vomiting within five hours after dosing, and meeting exclusion criteria. Investigators could include a subject excluded from the previous test period if appropriate.

Number of Subjects: 9

Schedule:
Screening procedures included informed consent, inclusion and exclusion criteria, medical history, medication history, demographics, body measurements, vital signs, ECG, physical examination, and clinical laboratory tests (including drug screen and pregnancy test).
The study consisted of three test periods separated by 35-day washout periods. Investigators randomized subjects to one of three treatment sequences. During each test period, investigators confined subjects from at least 10 hours prior to drug administration until after the 48-hour blood collection in each test period. Investigators collected blood samples during each test period at 0.500 hour, -0.250 hour and within five minutes (0 hour) prior to dosing, and at 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0, and 48.0 hours post-dose. The final safety visit was one month after the last dose of levothyroxine.

Test Products:
Refer to Table 4.

Table 4: Test Products (Study 140143 – 14CDN/T405)

<table>
<thead>
<tr>
<th>Product Identification</th>
<th>Test*</th>
<th>Reference-1</th>
<th>Reference-2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Company Responsible For Manufacturing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch/Lot Number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturing Date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expiration Date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>150 µg/mL</td>
<td>150 µg</td>
<td>100 µg/mL</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Oral solution (1 mL per single-dose ampule)</td>
<td>Capsule</td>
<td>Oral solution (1 mL per single-dose ampule)</td>
</tr>
<tr>
<td>Bio-batch Size</td>
<td>20 ampules</td>
<td>20 capsules</td>
<td>20 ampules</td>
</tr>
<tr>
<td>Production Batch Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>99.2%</td>
<td>98.2%</td>
<td>100.6%</td>
</tr>
</tbody>
</table>

Content Uniformity (mean, % CV):
- Test: 99.2%; AV = 3.6
- Reference-1: 99.0%; AV = 5.5
- Reference-2: 100.6%; AV = 1.7

Dosing Procedures for Test Product:
Investigators hypothesized that the previous study (Study 130284) failed to demonstrate bioequivalence of levothyroxine sodium oral solution to Tirosint capsules due to incomplete emptying of the unit-dose ampules during administration.
Investigators revised the dosing instructions for this study as follows:

- Remove the cap with ampule in vertical position (cap on top)
- Invert the ampule over 140 mL water in a container (glass or cup)
- Squeeze the ampule slowly between the thumb and first finger
- Release pressure for several seconds
- Repeat squeezing at least three times until no more liquid leaks from the ampule
- Rinse the container with 50 mL water twice and drink both times

Additionally, the pharmacy team weighed the ampules full and empty to verify total delivery of the medication.

Restrictions:
Prohibited foods and substances (24 hours to one week prior to dosing, depending on the substance) included poppy seeds, xanthine derivatives, natural supplements, grapefruit, star fruit, pomegranate, pineapple, pomelo, psyllium, walnuts, and alcohol.

Prior and concomitant medications:
The protocol prohibited prescription and over-the-counter medications except for management of adverse events.

Blinding:
None – open-label study

Assessment of Compliance:
Direct supervision of dosing

Efficacy Variables:
None

Safety Assessments:
Adverse Events, Vital Signs, ECG, clinical laboratory

Drug concentration measurements:
During each test period, investigators collected 19 blood samples at -0.500 hour, -0.250 hour and within five minutes (0 hour) prior to drug administration and 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0, and 48.0 hours post-dose.

Bioavailability:
Investigators calculated the following PK parameters
- $C_{\text{max}}$: maximum observed concentration
- $T_{\text{max}}$: time of observed $C_{\text{max}}$
Clinical Review
John Sharretts, M.D.
NDA 206977
Tirosint-SOL (levothyroxine sodium oral solution)

- AUC\(_{0-48}\): area under the concentration-time curve from time zero to the time of the last measureable concentration.

**Statistical Methods:**
Demographics – descriptive statistics
Safety – descriptive statistics
Pharmacokinetics:
- Analysis of variance (ANOVA)
  - Log transformed AUC\(_{0-48}\) and \(C_{\text{max}}\)
  - Untransformed \(T_{\text{max}}\)
  - Alpha 0.05
  - Factors: Sequence, subject, period, and treatment
- Ratios of least-squares means (A/B and C/B)
  - 90% geometric confidence intervals for each treatment comparison

**Study 140161 – 14CDN/T403 (Study 140161)**

**Title:** Randomized, Open-Label, 3-Way Crossover Comparative Bioavailability Study of Levothyroxine Sodium Oral Solution (Test) Administered With and Without Water and Tirosint Capsules (Reference) Following a Single Oral Dose of 600 µg in Healthy Subjects Under Fasting Conditions

**Design:**
Single center, randomized, single-dose, open-label, three-way crossover comparative bioavailability study

**Objectives:**
The primary objective was to compare the rate and extent of absorption of levothyroxine sodium oral solution 150 mcg unit-dose ampules administered with water (Test, Treatment A) versus Tirosint 150 mcg capsules (Reference, Treatment C) administered as a 600 mcg oral dose under fasting conditions.

The secondary objective was to compare the rate and extent of absorption of levothyroxine sodium oral solution 150 mcg unit-dose ampules administered without water (Test, Treatment B) versus levothyroxine sodium oral solution 150 mcg unit-dose ampules administered with water (Test, Treatment A), administered as a 600 mcg oral dose under fasting conditions.

**Study Population:**
Healthy adult subjects, 18 to 50 years

**Key inclusion criteria**
- Non-smoker or moderate smoker
Clinical Review
John Sharretts, M.D.
NDA 206977
Tirosint-SOL (levothyroxine sodium oral solution)

- Body mass index (BMI) > 18.5 kg/m² and < 30.0 kg/m²
- Body weight > 50 kg (males) and > 45 kg (females)
- Acceptable non-hormonal contraception (females of childbearing potential)

Key exclusion criteria
- Clinically significant abnormal laboratory results
- Positive pregnancy test or currently breastfeeding
- ECG or vital sign abnormalities
- History of alcohol or drug abuse within one year or positive drug screen
- Use of contraindicated medications
- Plasma donation within seven days, blood donation or blood loss up to 499 mL within 30 days or over 499 mL within 56 days

Withdrawal and re-entry criteria
Investigators could withdraw subjects for various reasons, including adverse reactions, non-compliance, protocol deviations, unscheduled concomitant medications, vomiting within five hours after dosing, and meeting exclusion criteria. Investigators could include a subject excluded from the previous test period if appropriate.

Number of Subjects: 36

Schedule:
Screening procedures included informed consent, inclusion and exclusion criteria, medical history, medication history, demographics, body measurements, vital signs, ECG, physical examination, and clinical laboratory tests (including drug screen and pregnancy test).

The study consisted of three test periods separated by 35-day washout periods. Investigators randomized subjects to one of three treatment sequences. During each test period, investigators confined subjects from at least 10 hours prior to drug administration until after the 48-hour blood collection in each study period. Investigators collected blood samples for each period at -0.500 hour, -0.250 hour and within five minutes (0 hour) prior to dosing, and at 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0, and 48.0 hours post-dose.

Test Products:
Refer to Table 5.
Table 5: Test Products (Study 140161 – 14CDN/T403)

<table>
<thead>
<tr>
<th>Product</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Identification</td>
<td>A and B</td>
<td>C</td>
</tr>
<tr>
<td>Product Name</td>
<td>Levothyroxine sodium oral solution</td>
<td>Tirosint® (levothyroxine sodium)</td>
</tr>
<tr>
<td>Company Responsible For Manufacturing</td>
<td>IBSA Institut Biochimique SA, Switzerland</td>
<td>IBSA Institut Biochimique SA, Switzerland</td>
</tr>
<tr>
<td>Batch/Lot Number</td>
<td>140701</td>
<td>140710</td>
</tr>
<tr>
<td>Manufacturing Date</td>
<td>July 2014</td>
<td>July 2014</td>
</tr>
<tr>
<td>Expiration Date</td>
<td></td>
<td>(8)(4)</td>
</tr>
<tr>
<td>Strength</td>
<td>150 µg</td>
<td>150 µg</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Oral solution, unit-dose ampule</td>
<td>Capsule</td>
</tr>
<tr>
<td>Bio-batch Size</td>
<td>Kg</td>
<td>capsules</td>
</tr>
<tr>
<td>Production Batch Size</td>
<td>Kg</td>
<td>(8)(14) capsules</td>
</tr>
<tr>
<td>Potency</td>
<td>99.6%</td>
<td>99.4%</td>
</tr>
<tr>
<td>Dose Administered</td>
<td>4 x 150 µg</td>
<td>4 x 150 µg</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td></td>
</tr>
</tbody>
</table>

**Dosing Procedures:**
Subjects self-administered test or reference medications following a supervised overnight fast of at least 10 hours. Subjects administered Treatments A (Test) and C (Reference) with 240 mL water and Treatment B (Test) without water.

**Treatment A (Oral solution administered with water)**
- Remove the cap with ampule in vertical position (cap on top)
- Invert the ampule over 140 mL water in a container (glass or cup)
- Squeeze the ampule slowly between the thumb and first finger
- Release pressure for several seconds
- Repeat squeezing at least five times until no more liquid leaks from the ampule
- Stir solution with a stick in the container and drink
- Rinse the container with 50 mL water twice and drink both times

**Treatment B (Oral solution administered without water)**
- Remove the cap with ampule in vertical position (cap on top)
- Invert the ampule over subject’s mouth
- Squeeze the ampule slowly between the thumb and first finger
- Release pressure for several seconds
- Repeat squeezing at least five times until no more liquid leaks from the ampule
For both Treatments A and B, the pharmacy team weighed the ampules full and empty to verify total delivery of the medication.

*Treatment C (Capsules)*

Subjects swallowed four capsules: one or two at a time with 240 mL water.

**Restrictions:**
Prohibited foods and substances (24 hours to one week prior to dosing, depending on the substance) included poppy seeds, xanthine derivatives, natural supplements, grapefruit, star fruit, pomegranate, pineapple, pomelo, psyllium, walnuts, and alcohol.

**Prior and concomitant medications:**
The protocol prohibited prescription and over-the-counter medications except for management of adverse events.

**Blinding:**
None – open-label study

**Assessment of Compliance:**
Direct supervision of dosing

**Efficacy Variables:**
None

**Safety Assessments:**
Adverse Events, Vital Signs, ECG, clinical laboratory

**Drug concentration measurements:**
During each test period, investigators collected 19 blood samples at -0.500 hour, -0.250 hour and within five minutes (0 hour) prior to drug administration and 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 24.0, and 48.0 hours post-dose.

**Bioavailability:**
Investigators calculated the following PK parameters
- $C_{\text{max}}$: maximum observed concentration
- $T_{\text{max}}$: time of observed $C_{\text{max}}$
- $\text{AUC}_{0-48}$: area under the concentration-time curve from time zero to the time of the last measurable concentration.

**Statistical Methods:**
Demographics – descriptive statistics
Safety – descriptive statistics

Reference ID: 4023308
Pharmacokinetics:
- Linear model analysis of variance (ANOVA)
  - Log-transformed AUC_{0-48} and C_{max}
  - Untransformed T_{max}
  - Alpha 0.05
  - Factors: Sequence, subject, period, and treatment
- Ratios of least-squares means (A/C and B/A)
  - 90% geometric confidence intervals for each treatment comparison
- Definition of bioequivalence (A/C)
  - Baseline-corrected total levothyroxine ratio of least square means
  - 90% confidence interval within 80.00% and 125.00%

Assumptions for sample size calculation
- Intra-subject coefficients of variation (CV) 19% (AUC) and 16% (C_{max})
- Ratio of AUC and C_{max}: within 0.925 and 1.08
- 90% power

Calculated sample size: 32 subjects
- 36 subjects included to account for dropouts

6 Review of Efficacy

Efficacy Summary
The Applicant is seeking marketing authorization through a 505(b)(2) New Drug Application relying on FDA findings of safety and efficacy for the reference listed drugs, Tirosint (levothyroxine sodium capsules) NDA 021924 (for doses between 13 mcg and 150 mcg), and Synthroid (levothyroxine sodium) tablets NDA 021402 (for the 175 mcg and 200 mcg doses and for pediatric patients under six years old). The Applicant completed one pivotal bioavailability study (Study 140161 – 14 CDN/T403) to establish bioequivalence between the new levothyroxine sodium oral solution formulation and Tirosint 150 mcg capsules.

The Applicant did not conduct any new clinical efficacy studies to support the application. In Study 140161, both test products (levothyroxine sodium oral solution administered with water, and levothyroxine sodium oral solution administered without water) met the pre-specified criteria for demonstration of bioequivalence with the reference product Tirosint capsules. Refer to the clinical pharmacology review for analysis of the results of the pivotal study.
6.1 Indication

The Applicant proposes the following indications:

- Hypothyroidism: TIROSINT-SOL is indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism.

- Pituitary Thyrotropin-Stimulating Hormone (TSH) Suppression: TIROSINT-SOL is indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

6.1.1 Methods

The Applicant did not submit any clinical efficacy studies. The Applicant completed one pivotal bioavailability study to establish the bioequivalence of Tirosint-SOL (levothyroxine sodium) oral solution with Tirosint (levothyroxine sodium) capsules in order to create a scientific bridge between its product and the reference listed drug. The Applicant submitted a 505(b)(2) application and intends to rely on previous FDA findings of safety and efficacy of the reference listed drugs.

6.1.2 Demographics

*Study 130284 - 13CDN/T406*

Table 6 summarizes the demographics and baseline characteristics of the Safety Population.
Table 6: Demographics and Baseline Characteristics Study 130284 – 13CDN/T406 (Safety Population)

<table>
<thead>
<tr>
<th>Category</th>
<th>Safety Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± SD 35 ± 10</td>
</tr>
<tr>
<td></td>
<td>Range 19 - 50</td>
</tr>
<tr>
<td>Median</td>
<td>34</td>
</tr>
<tr>
<td>Age Groups</td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>0</td>
</tr>
<tr>
<td>18-40</td>
<td>23 (63.9%)</td>
</tr>
<tr>
<td>41-64</td>
<td>13 (36.1%)</td>
</tr>
<tr>
<td>65-75</td>
<td>0</td>
</tr>
<tr>
<td>&gt;75</td>
<td>0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (58.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (41.7%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>Black/African American</td>
<td>2 (5.6%)</td>
</tr>
<tr>
<td>White</td>
<td>34 (94.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic</td>
<td>33 (91.7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean ± SD 25.35 ± 2.96</td>
</tr>
<tr>
<td></td>
<td>Range 19.48 - 29.59</td>
</tr>
<tr>
<td>Median</td>
<td>25.23</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean ± SD 169.5 ± 10.3</td>
</tr>
<tr>
<td></td>
<td>Range 151.5 - 191.0</td>
</tr>
<tr>
<td>Median</td>
<td>168.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean ± SD 73.38 ± 14.19</td>
</tr>
<tr>
<td></td>
<td>Range 46.50 - 107.40</td>
</tr>
<tr>
<td>Median</td>
<td>75.45</td>
</tr>
</tbody>
</table>

N: Number of observations; SD: Standard deviation; BMI: Body Mass Index.
Other: Multi-racial, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander.

Source: Applicant Table 14.1.1-1, Clinical Study Report, Study 130284

Study 140143 – 14CDN/T405

Table 7 summarizes the demographics and baseline characteristics of the Safety Population.
Table 7: Demographics and Baseline Characteristics Study 140143 – 14CDN/T405 (Safety Population)

<table>
<thead>
<tr>
<th>Category</th>
<th>Safety Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Age Groups</td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>0</td>
</tr>
<tr>
<td>18-40</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>41-64</td>
<td>5 (55.6%)</td>
</tr>
<tr>
<td>65-75</td>
<td>0</td>
</tr>
<tr>
<td>&gt;75</td>
<td>0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (66.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>8 (88.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic</td>
<td>7 (77.8%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
</tbody>
</table>

N: Number of observations; SD: Standard deviation; BMI: Body Mass Index.
Other: Multi-racial, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander.

Source: Applicant Table 14.1.1-1, Clinical Study Report, Study 140143

Study 140161 – 14CDN/T403

Table 8 summarizes the demographics and baseline characteristics of the Safety Population.
Table 8: Demographics and Baseline Characteristics Study 140161 – 14CDN/T403 (Safety Population)

<table>
<thead>
<tr>
<th>Category</th>
<th>Safety Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=36</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean = SD</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>Range</td>
<td>23 - 50</td>
</tr>
<tr>
<td>Median</td>
<td>34</td>
</tr>
<tr>
<td>Age Groups</td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>0</td>
</tr>
<tr>
<td>18-40</td>
<td>23 (63.9%)</td>
</tr>
<tr>
<td>41-64</td>
<td>13 (36.1%)</td>
</tr>
<tr>
<td>65-75</td>
<td>0</td>
</tr>
<tr>
<td>&gt;75</td>
<td>0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (50.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (50.0%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>Black/African American</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>White</td>
<td>33 (91.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic</td>
<td>34 (94.4%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (5.6%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>Mean = SD</td>
<td>24.90 ± 3.15</td>
</tr>
<tr>
<td>Range</td>
<td>19.54 - 29.93</td>
</tr>
<tr>
<td>Median</td>
<td>24.95</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
</tr>
<tr>
<td>Mean = SD</td>
<td>168.9 ± 7.7</td>
</tr>
<tr>
<td>Range</td>
<td>156.5 - 186.0</td>
</tr>
<tr>
<td>Median</td>
<td>167.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Mean = SD</td>
<td>71.40 ± 12.51</td>
</tr>
<tr>
<td>Range</td>
<td>52.70 - 103.20</td>
</tr>
<tr>
<td>Median</td>
<td>71.85</td>
</tr>
</tbody>
</table>

N: Number of observations; SD: Standard deviation; BMI: Body Mass Index. Other: Multi-racial, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander.

Source: Applicant Table 14.1.1-1, Clinical Study Report, Study 140161

6.1.3 Subject Disposition

Study 130284 - 13CDN/T406

Screened: 49
Enrolled: 40
Randomized: 36 (safety population)
Completed: 31
PK population:
- A versus C 30
- B versus A 32
Discontinuations:
Three subjects withdrew from at least one test period due to personal reasons. Investigators withdrew one subject due to inability to place a functional catheter. Investigators withdrew one subject due to non-compliance (unscheduled medication).

Protocol Deviations:
Investigators conducted additional analyses of residual liquid in the unit-dose ampules that suggested that subjects did not receive the full dose of oral solution despite following the dosing instructions described in the protocol.

One subject ingested only three of four capsules during Period 1. Investigators excluded the subject’s data for this test period. Additional reported protocol deviations were minor and unlikely to affect the study results.

Study 140143 – 14CDN/T405

Screened: 26
Enrolled: 12
Randomized: 9 (safety population)
Completed: 8
PK population: 8

Discontinuations:
One subject withdrew prior to test Period 2 due to a significant adverse event (Atrioventricular block, first degree).

Protocol Deviations:
Investigators reported minor time deviations in blood sample collections.

Study 140161 – 14CDN/T403

Screened: 78
Enrolled: 43
Randomized: 36 (safety population)
Completed: 31
PK population:
- A versus C 34
- B versus A 32

Discontinuations:
Four subjects withdrew from at least one test period for personal reasons. Investigators withdrew one subject due to a significant AE (Alanine aminotransferase increased).
Protocol Deviations:
Investigators reported minor deviations related to dosing for six subjects, and minor deviations related to collection or handling of blood samples for nine subjects. Additional protocol deviations were minor and unlikely to affect the results.

6.1.4 Analysis of Primary Endpoint(s)

Study 130284 - 13CDN/T406

The Applicant submitted analysis of the pharmacokinetic parameters $\text{AUC}_{0-48}$, $C_{\text{max}}$, and $T_{\text{max}}$ for baseline-corrected levothyroxine for levothyroxine sodium oral solution with water (Treatment A), levothyroxine sodium oral solution without water (Treatment B), and Tirosint with water (Treatment C). Table 9 summarizes ratios and 90% geometric confidence intervals for $\text{AUC}_{0-48}$ and $C_{\text{max}}$ for baseline-corrected levothyroxine. Refer to the clinical pharmacology review for complete analysis of the pharmacokinetic results.

Table 9: Ratios and 90% Geometric Confidence Intervals for $\text{AUC}_{0-48}$ and $C_{\text{max}}$ for Baseline-Corrected Levothyroxine (Study 130284 – 13CDN/T406)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Comparisons</th>
<th>Ratio$^1$</th>
<th>Lower</th>
<th>Upper</th>
<th>Intra-Subject CV</th>
<th>Inter-Subject CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-48}$</td>
<td>Test 1 (A) - Reference (C)</td>
<td>70.48%</td>
<td>55.40%</td>
<td>89.65%</td>
<td>60.87%</td>
<td>27.19%</td>
</tr>
<tr>
<td></td>
<td>Test 2 (B) - Test 1 (A)</td>
<td>100.93%</td>
<td>79.81%</td>
<td>127.63%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Test 1 (A) - Reference (C)</td>
<td>76.37%</td>
<td>66.44%</td>
<td>87.79%</td>
<td>33.39%</td>
<td>24.02%</td>
</tr>
<tr>
<td></td>
<td>Test 2 (B) - Test 1 (A)</td>
<td>94.91%</td>
<td>82.85%</td>
<td>108.73%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Calculated using least-squares means according to the formula: $e^{(\text{DIFFERENCE})} \times 100$.
$^2$ 90% Geometric Confidence Interval using In-transformed data.

Source: Applicant Table 11.4.1-3, Clinical Study Report, Study 130284

Reviewer Comment: The Applicant failed to demonstrate bioequivalence between the test product (levothyroxine sodium oral solution administered with water) and the reference product (Tirosint capsules administered with water)
Clinical Review
John Sharretts, M.D.
NDA 206977
Tirosint-SOL (levothyroxine sodium oral solution)

Study 140143 – 14CDN/T405

The Applicant submitted analysis of the pharmacokinetic parameters \( \text{AUC}_{0-48}, \ C_{\text{max}}, \) and \( \text{T}_{\text{max}} \) for baseline-corrected levothyroxine for levothyroxine sodium oral solution (Treatment A), Tirosint capsules (Treatment B), and Tirosint oral solution (Treatment C). Table 10 summarizes ratios and 90% geometric confidence intervals for \( \text{AUC}_{0-48} \) and \( \text{C}_{\text{max}} \) for baseline corrected levothyroxine. Refer to the clinical pharmacology review for complete analysis of the pharmacokinetic results.

Table 10: Ratios and 90% Geometric Confidence Intervals for \( \text{AUC}_{0-48} \) and \( \text{C}_{\text{max}} \) for Baseline-Corrected Levothyroxine (Study 140143 – 14CDN/T405)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Comparisons</th>
<th>Ratio(^1)</th>
<th>Lower</th>
<th>Upper</th>
<th>Intra-Subject CV</th>
<th>Inter-Subject CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{0-48} )</td>
<td>Test (A) – Reference 1 (B)</td>
<td>101.37%</td>
<td>91.45%</td>
<td>112.36%</td>
<td>11.50%</td>
<td>14.61%</td>
</tr>
<tr>
<td></td>
<td>Reference 2 (C) – Reference 1 (B)</td>
<td>112.00%</td>
<td>101.04%</td>
<td>124.15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{C}_{\text{max}} )</td>
<td>Test (A) – Reference 1 (B)</td>
<td>92.45%</td>
<td>84.31%</td>
<td>101.39%</td>
<td>10.30%</td>
<td>12.31%</td>
</tr>
<tr>
<td></td>
<td>Reference 2 (C) – Reference 1 (B)</td>
<td>106.37%</td>
<td>97.00%</td>
<td>116.65%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Calculated using least-squares means according to the formula: \( e^{(\text{Difference})} \times 100. \)

\(^2\) 90% Geometric Confidence Interval using In-transformed data.

Source: Table 11.4.2.3-3, Clinical Study Report, Study 14CDN/T405

Reviewer comment: The Applicant demonstrated preliminary evidence of bioequivalence between the test product (levothyroxine sodium oral solution) and the reference products (Tirosint capsules, Tirosint oral solution) to support the pivotal bioequivalence study (Study 140161).

Study 140161 – 14CDN/T403

The Applicant submitted analysis of the pharmacokinetic parameters \( \text{AUC}_{0-48}, \ C_{\text{max}}, \) and \( \text{T}_{\text{max}} \) for baseline-corrected levothyroxine for levothyroxine sodium oral solution with water (Treatment A), levothyroxine sodium oral solution without water (Treatment B), and Tirosint capsules (Treatment C). Table 11 summarizes ratios and 90% geometric confidence intervals for \( \text{AUC}_{0-48} \) and \( \text{C}_{\text{max}} \) for baseline corrected levothyroxine. The Applicant is relying on results from this study to demonstrate bioequivalence between its new product, Tirosint-SOL and the reference listed drug, Tirosint (levothyroxine sodium capsules). Refer to the clinical pharmacology review for complete analysis of the pharmacokinetic results.
Table 11: Ratios and 90% Geometric Confidence Intervals for AUC$_{0-48}$ and $C_{\text{max}}$ for Baseline-Corrected Levothyroxine (Study 140161 – 14CDN/T403)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Comparisons</th>
<th>Ratio$^1$</th>
<th>Lower</th>
<th>Upper</th>
<th>Intra-Subject CV</th>
<th>Inter-Subject CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-48}$</td>
<td>Test-1(A) – Reference (C)</td>
<td>98.47%</td>
<td>94.97%</td>
<td>102.11%</td>
<td>8.99%</td>
<td>22.42%</td>
</tr>
<tr>
<td></td>
<td>Test-2(B) – Test-1(A)</td>
<td>102.72%</td>
<td>98.98%</td>
<td>106.60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Test-1(A) – Reference (C)</td>
<td>95.33%</td>
<td>91.97%</td>
<td>98.82%</td>
<td>8.91%</td>
<td>21.36%</td>
</tr>
<tr>
<td></td>
<td>Test-2(B) – Test-1(A)</td>
<td>99.26%</td>
<td>95.70%</td>
<td>102.99%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Calculated using least-squares means according to the formula: $e$^(DIFFERENCE) X 100.
$^2$ 90% Geometric Confidence Interval using In-transformed data.

Source: Table 11.4.2.3-3, Clinical Study Report, Study 14CDN/T403

Reviewer comment: The Applicant demonstrated bioequivalence between the test product (levothyroxine sodium oral solution) and the reference product (Tirosint capsules) based on the reported results. The Applicant also demonstrated equivalence between the two dosing methods (with and without water) based on these reported results. Refer to the Clinical Pharmacology review for full analysis of the study.

6.1.5 Analysis of Secondary Endpoints(s)

None

6.1.6 Other Endpoints

Refer to the Clinical Pharmacology Review for complete analysis of pharmacokinetic results in the three studies.

6.1.7 Subpopulations

None

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The Applicant submitted pooled safety data from three biopharmaceutical studies in support of the application. The Applicant reported no deaths or non-fatal serious adverse events. Investigators withdrew two subjects from studies as a precautionary measure due to adverse events, and both events resolved spontaneously. The most common treatment-emergent adverse events were headache and somnolence. Treatment-emergent adverse events were consistent with the known safety profile of approved levothyroxine sodium products. The submitted studies did not identify any new safety issues.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant completed three bioequivalence studies to support approval of Tirosint-SOL (levothyroxine sodium oral solution). The first study (Study 130284 - 13CDN/T406) failed to demonstrate bioequivalence of the test product to the reference product, Tirosint (levothyroxine sodium capsules). Investigators concluded that the procedure for emptying the unit-dose ampules was inadequate after discovering a significant amount of residual drug product in the use ampules after dosing. After developing a new procedure for emptying the ampules, the investigators conducted a pilot study (Study 140143 – 14CDN/T405) to evaluate bioequivalence of the test product to Tirosint capsules and to a different oral solution formulation, Tirosint (levothyroxine sodium oral solution). After the pilot study demonstrated a favorable outcome, investigators conducted a new pivotal study (Study 140161 – 14CDN/T403) comparing the test product administered with and without water to the reference product, Tirosint capsules.
7.1.2 Categorization of Adverse Events

Investigators monitored subjects for adverse events (AEs) from the time of informed consent until the final study visit. The safety population included all subjects who received at least one dose of study medication. Investigators elicited AEs through questioning, spontaneous reports, and significant abnormal results of vital signs, physical examination, ECG, and clinical laboratory.

Investigators defined a treatments-emergent AE (TEAE) as an AE that began on or after the first study drug administration or an AE that began before the first study drug administration but worsened in severity or duration after study drug administration. Investigators defined a serious AEs (SAE) as any event that was fatal, life-threatening, resulted in persistent or significant disability or incapacity, required in-patient or prolonged hospitalization, resulted in congenital abnormalities or birth defects, required medical or surgical intervention to prevent one of the previously listed outcomes, or resulted in suspected transmission of an infectious agent via a medicinal product. Investigators defined a significant AE as any event (other than those reported as serious) that led to an intervention, including withdrawal of treatment, dose reduction, or significant additional concomitant therapy.

Investigators categorized all AEs using Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0 (Study 130284 and Study 140143) and Version 17.1 (Study 140161). For the pooled safety analysis, investigators recoded AEs from Study 130284 and 140143 with Version 17.1 without any changes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant submitted pooled safety data sets for Study 130284, Study 140143, and Study 140161 for review. The design of the three studies was very similar. Each study was a randomized, single-dose, open-label, three-way crossover, comparative bioavailability study. In all three studies, each subject received a maximum of three doses of 600 mcg of levothyroxine separated by 35-day washout periods. The schedule and procedures for collection of safety data were nearly identical for the three studies. The major differences were the additional reference product in Study 140143, Tirosint oral solution (formulation), and the earlier version of MedDRA used in Study 130284 and 140143.

The pooled safety data set consists of four treatment groups. Treatment A is the test product, levothyroxine sodium oral solution, administered with water. Treatment B is the test product, levothyroxine sodium oral solution, administered without water. Treatment C is the reference product, Tirosint capsules. Treatment D is the reference product Tirosint oral solution (formulation). Treatments B and C in Study
Clinical Review  
John Sharretts, M.D.  
NDA 206977  
Tirotsint-SOL (levothyroxine sodium oral solution)

140143 correspond to Treatments C and D, respectively, in the pooled data set. Study 140143 did not assess the test product, levothyroxine sodium oral solution without water, but instead included the two reference arms.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All subjects in the safety population received at least one dose and up to three doses of levothyroxine. Table 12 summarizes the number of subjects receiving each treatment in each individual study and the pooled data set.

Table 12: Subject Exposure by Treatment (by Study and Overall)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Treatment C</th>
<th>Treatment D</th>
</tr>
</thead>
<tbody>
<tr>
<td>130284</td>
<td>34</td>
<td>33</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>140143</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>140161</td>
<td>35</td>
<td>34</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>77</td>
<td>67</td>
<td>74</td>
<td>9</td>
</tr>
</tbody>
</table>

A=IBSA Institut Biochimique SA, Switzerland, levothyroxine sodium oral solution (LSOS) 4 x 150 μg unit dose ampules administered with water.  
B=IBSA Institut Biochimique SA, Switzerland, levothyroxine sodium oral solution (LSOS) 4 x 150 μg unit dose ampules administered without water.  
C=IBSA Institut Biochimique SA, Switzerland (Tirotsint®), levothyroxine sodium 4 x 150 μg capsules.  
D=IBSA Farmaceutici Italia Srl, Italy (Tirotsint® oral solution), levothyroxine sodium 6 x 100 μg unit-dose ampules.

Source: Applicant Table 2, Integrated Summary of Safety

7.2.2 Explorations for Dose Response

Not applicable

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Investigators obtained clinical laboratory samples (biochemistry, hematology, endocrine and urinalysis) for each subject at screening, before dosing of Periods 2 and 3, and at the final study visit in all three studies. Investigators performed a urine pregnancy test at screening and study exit, and serum pregnancy test prior to dosing in each test period.
7.2.5 Metabolic, Clearance, and Interaction Workup
Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class
Not applicable

7.3 Major Safety Results

7.3.1 Deaths
The Applicant reported no deaths in the three studies included in the pooled data set.

7.3.2 Nonfatal Serious Adverse Events
The Applicant reported no serious adverse events in the three studies included in the pooled data set.

7.3.3 Dropouts and/or Discontinuations
Two subjects discontinued due to AEs. Investigators withdrew one subject in Study 140143 after treatment with Tirosint oral solution (formulation) for the AE: Atrioventricular block first degree. Investigators categorized the AE as mild and unrelated to study drug, and the AE resolved spontaneously. Investigators withdrew one subject in Study 140161 after treatment with levothyroxine oral solution with water for the AE: Alanine aminotransferase increased. Investigators categorized the AE as mild and possibly related to study drug, and the AE resolved spontaneously. Investigators did not classify either event as an SAE, because study withdrawal was precautionary.

7.3.4 Significant Adverse Events
One subject in Study 140161 experienced the AE: Sinusitis following treatment with levothyroxine sodium oral solution without water. The AE was recorded at study exit and did not lead to study withdrawal. Investigators categorized the event as mild, remote in relation to study drug, and significant due to the need for additional concomitant medication.
7.3.5 Submission Specific Primary Safety Concerns

Adverse reactions associated with levothyroxine are well-known and primarily those of hypothyroidism due to therapeutic overdose. The studies in this submission did not identify any new safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 130284 – 13CDN/T406

Twenty of the 36 subjects in the safety population experienced 54 treatment-emergent AEs (TEAEs), of which investigators graded 52 mild and 2 moderate. The most common TEAEs reported were headache, nasopharyngitis, and somnolence.

7.4.2 Laboratory Findings

The Applicant submitted laboratory results for subjects in the three studies. Investigators collected general biochemistry, hematology, and urinalysis at screening, before each treatment period, and at study exit. Investigators collected endocrinology at those time points plus an additional collection at the one month follow-up visit. Two subjects were missing laboratories for at least one visit (lost to follow-up). One subject did not have laboratory results for either study exit or the safety follow-up visit, and one subject did not have laboratory results for the safety follow-up.

Biochemistry

Abnormal results occurred for most parameters. The majority of the abnormalities were slightly outside the normal reference range and not significant. Plasma glucose was elevated in 22 subjects on 28 collections (range 6.1 mmol/L to 11.0 mmol/L), including 13 values greater than or equal to 7.0 mmol/L. All elevated glucose values occurred at check in for test Periods 2 and 3, and were non-fasting. All fasting glucose values (screening, study exit) were normal.

One subject in Study 140161 experienced elevated ALT 106 U/L (normal 0-41) prior to test Period 3. Investigators coded this laboratory abnormality as the AE: Alanine aminotransferase elevated and withdrew the subject from the study (refer to Section 7.3.4). The ALT level returned to normal at an unscheduled visit five days later.

Endocrinology

TSH level was below the normal range on 36 collections in 33 subjects. Among these, 33 abnormal values occurred at study exit (48 hour after dosing in test Period 3). One subject in Study 140161 also had TSH 0.37 mU/L (normal range 0.47-4.64) at screening.
and 0.4 mU/L at test Period 3. The subject had a normal TSH on the unscheduled repeat collection at screening (Free T₄ and Total T₃ were normal at screening), and normal thyroid function tests at the safety follow-up visit.

Two subjects had elevated TSH at the safety follow-up visit (one month after final dose), but normal TSH at unscheduled follow up two to four weeks later. One subject in Study 140143 had elevated TSH 7.58 mU/L at the safety follow-up visit but no additional follow up. One subject in Study 140161 had persistent elevation of TSH 8.03 mU/L at the follow-up visit and elevated TSH at two subsequent unscheduled follow-ups, both associated with low Free T₄. At the first unscheduled visit, two weeks after the safety visit, the TSH was 5.47 mU/L and Free T₄ was 11.4 pmol/L (11.5-22.7). At the second unscheduled visit, three weeks later, TSH was 5.72 mU/L and Free T₄ was 10.3 pmol/L. Investigators coded this subject with the AE: Thyroxine free decreased.

Ten subjects had Free T₄ above normal at study exit (48 hours after dosing), all of whom had normal Free T₄ at the one-month follow-up safety visit. Twelve low Free T₄ values occurred in seven subjects at various time points in the study. Five low values occurred at screening. For all five subjects, screening TSH and repeat Free T₄ at screening (unscheduled) were normal. Two subjects had low values at the safety follow-up visit, but normal TSH values. One subject, discussed above under TSH, had the remaining two low values at unscheduled follow-up visits.

Three subjects had Total T₃ slightly below normal. Other thyroid parameters were normal for these subjects, and follow up values were all normal.

**Hematology**

Abnormal results occurred for most parameters. Investigators did not consider any of the findings significant enough to code as an AE. Three subjects had at least one WBC count below normal, and seven subjects had at least one WBC value above normal. One subject had an elevated platelet count on three collections. No subjects had a low platelet count. Eighteen subjects had at least one value below the normal range for at least one of these three red blood cell parameters: hemoglobin, hematocrit, or red blood cells, whereas five subjects had at least one value above normal for one of the three parameters.

**Urinalysis**

The majority of subjects had at least one abnormal parameter on urinalysis on at least one collection. Investigators coded one AE: Red blood cells urine positive for one subject in Study 140161 who had 3-5 RBC/HPF on two collections. Four additional subjects had red blood cells in the urine not coded as an AE, and two subjects had white blood cells in the urine also not coded as an AE.
7.4.3 Vital Signs

Investigators performed vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) at screening and study exit. Investigators performed blood pressure and heart rate prior to dosing and 2, 4, 8, 12, and 24 hours post-dose, in each test period. Ten subjects had at least one elevation in diastolic BP above 89 mmHg, three subjects had at least one elevation of systolic BP above 139 mmHg, Seven subject had at least one decrease in systolic BP less than 90 mmHg, and six subjects had at least one elevation in heart rate > 99 beats per minute.

Investigators coded two TEAEs based on vital signs abnormalities. Investigators coded the AE: Heart rate increased for one subject in Study 140161 who had a heart rate recorded as high as 106 bpm after dosing in test Period 2. Investigators coded the AE: Blood pressure decreased for one subject in Study 130284 who had several low blood pressure readings after dosing in test Period 2, including a value of 86/56 mmHg.

7.4.4 Electrocardiograms (ECGs)

Investigators performed ECG at screening, pre-dose and 48-hours post-dose in each test period, and at study exit. Investigators identified an abnormality in at least one ECG in 46 subjects (for example sinus arrhythmia, right bundle branch block, early repolarization, sinus bradycardia, left axis deviation, and right axis deviation). Investigators judged most abnormalities as having no clinical significance. Investigators coded one subject in Study 140143 who had a PR interval as long as 244 msec with the AE: Atrioventricular block first degree. The AE resolved spontaneously within four days. Four subjects in Study 130284, one additional subject in Study 140143, and four subjects in 140161 had at least one ECG with first degree atrioventricular block, but investigators judged all as having no clinical significance. The vast majority had a PR interval between 200 msec and 220 msec on these recordings.

Reviewer comment: Adverse event reporting, clinical laboratory results, vital signs, and ECG findings did not identify any new safety concerns for levothyroxine oral solution.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable
7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
Not applicable

7.5.2 Time Dependency for Adverse Events
Not applicable

7.5.3 Drug-Demographic Interactions
Not applicable

7.5.4 Drug-Disease Interactions
Not applicable

7.5.5 Drug-Drug Interactions
Not applicable

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity
Not applicable

7.6.2 Human Reproduction and Pregnancy Data
Not applicable

7.6.3 Pediatrics and Assessment of Effects on Growth
Not applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound
Not applicable
Clinical Review
John Sharretts, M.D.
NDA 206977
Tirosint-SOL (levothyroxine sodium oral solution)

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Tirosint-SOL is not approved for marketing in any country or region.
9 Appendices

9.1 Literature Review/References


Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2016; 26: 1-133.


9.2 Labeling Recommendations

We will review the proposed label separately.

9.3 Advisory Committee Meeting

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN M SHARRETTS
12/06/2016

MARINA ZEMSKOVA
12/06/2016