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RESEARCH**

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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s) John Sharretts, M.D.
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Established Name Levothyroxine sodium
(Proposed) Trade Name Tirosint-SOL
Therapeutic Class Thyroid hormone
Applicant Institut Biochimique SA (IBSA)

Formulation(s) Oral solution
Dosing Regimen 13, 25, 50, 75, 88, 100, 112, 125,
137, 150, 175, and 200 mcg/mL
Indication(s) Hypothyroidism
Pituitary TSH Suppression
Intended Population(s) Adult, Pediatric

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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 or 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%.^{2,3,4} 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.⁵

1 Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woebler KA. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract.* 2012; 18: 988-1028.

2 Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). *Thyroid.* 2007; 17: 1211-23.

3 Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2002;87(2):489-499.

4 Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Wickham Survey. *Clin Endocrinol (Oxf).* 1995; 43: 55-68.

5 Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid.* 2014; 24: 1670-751.

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 radioiodine 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.⁶

2.1 Product Information

Tirosint-SOL (levothyroxine sodium oral solution) is a liquid formulation of levothyroxine dissolved in glycerol (b) (4) 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 1 (b) (4) 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 (b) (4) therapy in (b) (4) primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism.
- Pituitary Thyrotropin Stimulating Hormone (TSH) Suppression: as an adjunct to surgery and radioiodine 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 (b) (4), approved for marketing in Italy in February 2012 at strengths of 25, 50, 75, and 100 mcg/mL.

6 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

Brand Name	Application number	Manufacturer	Dosage Form
<i>Approved Levothyroxine Sodium Products</i>			
Levo-T	NDA 021342	Alara	Tablet
Levoxyl	NDA 021301	King	Tablet
Synthroid	NDA 021402	Abbvie	Tablet
Tirosint	NDA 021924 NDA 022121	IBSA	Capsule
Unithroid	NDA 021210	Jerome Stevens	Tablet
Levothyroxine sodium	ANDA 076187	Mylan	Tablet
<i>Approved Levothyroxine Sodium Products Not Currently Marketed</i>			
Levolet	NDA 021137	Lehigh Valley	Tablet
Thyro-Tabs (Levothroid)	NDA 021116	Lloyd	Tablet
Novothyrox	NDA 021292	Merck KGAA	Tablet
<i>Approved Liothyronine Products</i>			
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,

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 (b) (4) glycerol. 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 (b) (4) in the original formulation with regards to (b) (4) 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 (b) (4). 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) (b) (4). 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_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybeans. Dietary fiber decreases the bioavailability of T_4 . Absorption may also decrease with age. In addition, many drugs and foods affect T_4 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_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to T_3 . 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_4 is slowly eliminated. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3 , with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (r T_3). T_3 and r T_3 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_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age. T_4 is 99.96% bound to protein (TBG, TBPA, and TBA) and has a half-life of approximately 6-7 days. T_3 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

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

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

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.

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

Product	Tests	Reference
Treatment ID	A and B	C
Product Name	Levothyroxine sodium oral solution	Tirosint® (levothyroxine sodium)
Manufacturer	IBSA Institut Biochimique SA, Switzerland	IBSA Institut Biochimique SA, Switzerland
Batch/Lot No.	130802	130606
Manufacture Date	August 2013	June 2013
Expiration Date	(b) (4)	
Strength	150 µg/mL	150 µg
Dosage Form	Single-dose ampule (1 mL)	Capsule
Potency	(b) (4)	
Dose Administered	4 x 150 µg	4 x 150 µg
Route of Administration	Oral	Oral

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)

Product	Test*	Reference-1	Reference-2**
Treatment Identification	A	B	C
Product Name	Levothyroxine sodium oral solution	Tirosint® (levothyroxine sodium)	Tirosint® oral solution (levothyroxine sodium)
Company Responsible For Manufacturing	IBSA Institut Biochimique SA, Switzerland	IBSA Institut Biochimique SA, Switzerland	IBSA Institut Biochimique SA, Switzerland
Batch/Lot Number	130802	130606	140306
Manufacturing Date	August 2013	June 2013	March 2014
Expiration Date	(b) (4)		
Strength	150 µg/ mL	150 µg	100 µg/ mL
Dosage Form	Oral solution (1 mL per single-dose ampule)	Capsule	Oral solution (1 mL per single-dose ampule)
Bio-batch Size	(b) (4) ampules	(b) (4) capsules	(b) (4) ampules
Production Batch Size	ampules	capsules	ampules
Potency	(b) (4)		
Content Uniformity (mean, % CV)	99.2%; AV= 3.6	99.0%; AV=5.5	100.6%; AV=1.7
Dose Administered	4 x 150 µg	4 x 150 µg	6 x 100 µg
Route of Administration	Oral	Oral	Oral

AV: Acceptance value; CV: Coefficient of variation.

* (b) (4) formula; ** (b) (4) formula

Source: Applicant Table 9.4.2-1, Clinical Study Report, Study 140143

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_{max} : maximum observed concentration
- T_{max} : time of observed C_{max}

- 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_{max}
 - Untransformed T_{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 μ g 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

- 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)

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

AV: Acceptance value; CV: Coefficient of variation.

Source: Applicant Table 9.4.2-1, Clinical Study Report, Study 140161

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_{max} : maximum observed concentration
- T_{max} : time of observed C_{max}
- 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:

- 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 [REDACTED] (b) (4) [REDACTED] (b) (4) primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism. [REDACTED] (b) (4) [REDACTED]
- 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)

Category		Safety Population N=36
Age (years)	Mean ± SD	35 ± 10
	Range	19 - 50
	Median	34
Age Groups	<18	0
	18-40	23 (63.9%)
	41-64	13 (36.1%)
	65-75	0
	>75	0
Gender	Male	21 (58.3%)
	Female	15 (41.7%)
Race	Asian	0
	Black/African American	2 (5.6%)
	White	34 (94.4%)
	Other	0
Ethnicity	Not Hispanic	33 (91.7%)
	Hispanic	3 (8.3%)
BMI (kg/m ²)	Mean ± SD	25.35 ± 2.96
	Range	19.48 - 29.59
	Median	25.23
Height (cm)	Mean ± SD	169.5 ± 10.3
	Range	151.5 - 191.0
	Median	168.8
Weight (kg)	Mean ± SD	73.38 ± 14.19
	Range	46.50 - 107.40
	Median	75.45

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)

Category		Safety Population N=9
Age (years)	Mean ± SD	38 ± 11
	Range	20 - 49
	Median	43
Age Groups	<18	0
	18-40	4 (44.4%)
	41-64	5 (55.6%)
	65-75	0
	>75	0
Gender	Male	6 (66.7%)
	Female	3 (33.3%)
Race	Asian	1 (11.1%)
	Black/African American	0
	White	8 (88.9%)
	Other	0
Ethnicity	Not Hispanic	7 (77.8%)
	Hispanic	2 (22.2%)
BMI (kg/m ²)	Mean ± SD	25.05 ± 2.47
	Range	19.71 - 28.96
	Median	25.03
Height (cm)	Mean ± SD	169.8 ± 6.0
	Range	162.0 - 180.0
	Median	171.0
Weight (kg)	Mean ± SD	72.49 ± 9.80
	Range	52.70 - 84.90
	Median	73.20

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)

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

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 AUC₀₋₄₈, C_{max}, and T_{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 AUC₀₋₄₈ and C_{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 AUC₀₋₄₈ and C_{max} for Baseline-Corrected Levothyroxine (Study 130284 – 13CDN/T406)

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC ₀₋₄₈	Test 1 (A) - Reference (C)	70.48%	55.40%	89.65%	60.87%	27.19%
	Test 2 (B) - Test 1 (A)	100.93%	79.81%	127.63%		
C _{max}	Test 1 (A) - Reference (C)	76.37%	66.44%	87.79%	33.39%	24.02%
	Test 2 (B) - Test 1 (A)	94.91%	82.85%	108.73%		

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

² 90% Geometric Confidence Interval using ln-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).*

Study 140143 – 14CDN/T405

The Applicant submitted analysis of the pharmacokinetic parameters AUC₀₋₄₈, C_{max}, and T_{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 AUC₀₋₄₈ and C_{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 AUC₀₋₄₈ and C_{max} for Baseline-Corrected Levothyroxine (Study 140143 – 14CDN/T405)

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC ₀₋₄₈	Test (A)-Reference 1 (B)	101.37%	91.45%	112.36%	11.50%	14.61%
	Reference 2 (C)-Reference 1 (B)	112.00%	101.04%	124.15%		
C _{max}	Test (A)-Reference 1 (B)	92.45%	84.31%	101.39%	10.30%	12.31%
	Reference 2 (C)-Reference 1 (B)	106.37%	97.00%	116.65%		

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

² 90% Geometric Confidence Interval using ln-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 AUC₀₋₄₈, C_{max}, and T_{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 AUC₀₋₄₈ and C_{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 AUC₀₋₄₈ and C_{max} for Baseline-Corrected Levothyroxine (Study 140161 – 14CDN/T403)

Parameter	Treatment Comparisons	Ratio ¹	90% Geometric C.I. ²		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC ₀₋₄₈	Test-1 (A) - Reference (C)	98.47%	94.97%	102.11%	8.99%	22.42%
	Test-2 (B) - Test-1 (A)	102.72%	98.98%	106.60%		
C _{max}	Test-1 (A) - Reference (C)	95.33%	91.97%	98.82%	8.91%	21.36%
	Test-2 (B) - Test-1 (A)	99.28%	95.70%	102.99%		

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

² 90% Geometric Confidence Interval using ln-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 ((b) (4) 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 ((b) (4) formulation). Treatments B and C in Study

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)

Study	Treatment A	Treatment B	Treatment C	Treatment D
130284	34	33	32	0
140143	8	0	8	9
140161	35	34	34	0
Overall	77	67	74	9

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 (Tirosint®), levothyroxine sodium 4 x 150 µg capsules.

D=IBSA Farmaceutici Italia Srl, Italy (Tirosint® oral solution), levothyroxine sodium 6 x 100 µg unit-dose ampules (b)(4) formula).

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 ((b) (4) 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

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

Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). *Thyroid*. 2007; 17: 1211-23.

Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woeber KA. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012; 18: 988-1028.

Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002; 87: 489-499.

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.

Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid*. 2014; 24: 1670-751.

Sawin CT, Castelli WP, Hershman JM, McNamara P, Bacharach P. The aging thyroid. Thyroid deficiency in the Framingham Study. *Arch Intern Med*. 1985; 145: 1386- 1388.

Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Wickham Survey. *Clin Endocrinol (Oxf)*. 1995; 43: 55-68.

9.2 Labeling Recommendations

We will review the proposed label separately.

9.3 Advisory Committee Meeting

None

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/s/

JOHN M SHARRETTS
12/06/2016

MARINA ZEMSKOVA
12/06/2016

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 206977

Submission Date(s): 02/26/2016

Applicant: Institut Biochimique SA (IBSA)

Product: Tirosint-SOL

Reviewer: John Sharretts, M.D.

Date of Review: 12/06/2016

Covered Clinical Study (Name and/or Number): 140161,130284, 140143

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>13</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

¹ See [web address].

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/s/

JOHN M SHARRETT
12/06/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206977

**Applicant: Institut
Biochimique SA (IBSA)**

Stamp Date: 02/26/2016

Drug Name: Tirosint-SOL

**NDA/BLA Type: Type-3 New
Dosage Form**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			eCTD format
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	No clinical efficacy data submitted
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Bioavailability studies only
10.	Has the applicant submitted a benefit-risk analysis for the product?			X	No clinical efficacy data submitted
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?	X			Tirosint Synthroid
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			
14.	Describe the scientific bridge (e.g., BA/BE studies)	X			Bioequivalence studies
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms:			X	No clinical efficacy data submitted

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	been exposed at the dosage (or dosage range) believed to be efficacious?				
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v. 17.1
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths, dropouts, serious or severe AE.
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?		X		
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and			X	No clinical efficacy

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	complete for all indications requested?				studies
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No clinical efficacy data
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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/s/

JOHN M SHARRETTS
05/10/2016

MARINA ZEMSKOVA
05/10/2016