CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206977Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	206-977 S-0001 (b) (4)
Submission Dates	February 26, 2016 and June 1, 2016
Brand Name	Tirosint-SOL
Generic Name	Levothyroxine sodium
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	IBSA Institut Biochimique SA
Formulation; Strengths	Oral solution; 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 µg/mL
Relevant NDA	21-924 (Tirosint capsules)
Indications	Treat hypothyroidism and pituitary thyrotropin suppression

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1 Executive Summary

The sponsor seeks approval via the regulatory 505(b)(2) pathway for the 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 µg/mL strengths of levothyroxine sodium oral solution to treat hypothyroidism and pituitary thyrotropin-stimulating hormone suppression.

The same sponsor's Tirosint capsules (13, 25, 50, 75, 88, 100, 112, 125, 137, and 150 µg levothyroxine sodium) has approved indications to treat hypothyroidism and pituitary thyrotropin-stimulating hormone suppression.

Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 206-977's Clinical Pharmacology data submitted on February 26, 2016 and June 1, 2016 and finds them acceptable to support approval. Labeling recommendations are on Pages 10 – 13.

1.2 Post Marketing Requirement or Post Marketing Commitment

None.

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor submitted the results of the following 3 clinical pharmacology studies to support NDA 206-977:

- Study 130284 is a 3-way crossover relative bioavailability study of levothyroxine sodium oral solution (test) administered with and without water and Tirosint capsule (reference) following a single oral dose of 600 µg under fasting in healthy volunteers. Study 130284 failed because of incomplete dosing with residue left in the ampules.
- Study 140143 is a pilot 3-way crossover relative bioavailability study evaluating the rate and extent of absorption of 150 µg dosage strength levothyroxine sodium oral solution compared to 150 µg Tirosint capsules and 100 µg unit-dose ampules of the prototype (b) (4) formulation of levothyroxine sodium oral solution following a single oral dose of 600 µg under fasting in healthy volunteers.
- Study 140161 is a pivotal 3-way crossover relative bioavailability study of levothyroxine sodium oral solution (test) administered with and without water and Tirosint capsule (reference) following a single oral dose of 600 µg under fasting in healthy volunteers.

This reviewer did not review Studies 130284 and 140143 but reviewed Study 140161 instead.

Study 140161's results show the following:

- Levothyroxine sodium oral solution taken with water is bioequivalent to Tirosint capsule according to the baseline corrected levothyroxine C_{max} and AUC_{0-48h} parameters under fasting condition.
- Levothyroxine sodium oral solution taken without water is bioequivalent to Tirosint capsule according to the baseline corrected levothyroxine C_{max} and AUC_{0-48h} under fasting condition.
- Levothyroxine sodium oral solution taken with water is bioequivalent to Tirosint capsule according to the baseline uncorrected levothyroxine C_{max} and AUC_{0-48h} under fasting condition.
- Levothyroxine sodium oral solution taken without water is bioequivalent to Tirosint capsule according to the baseline uncorrected levothyroxine C_{max} and AUC_{0-48h} under fasting condition.

The clinically-tested levothyroxine sodium oral solution formulation is the same as the to-be-marketed levothyroxine sodium oral solution formulation . The sponsor studied the United States approved and marketed Tirosint capsules in Study 140161 as the reference product.

The sponsor requested a biowaiver for dosage-form proportionality study of levothyroxine formulations. See Biopharmaceutics reviewer's review for the request of biowaiver.

Tirosint 150 µg capsule is the reference listed drug for levothyroxine sodium oral solution 13 – 150 µg/mL strengths. Synthroid 300 µg tablet is the reference listed drug for levothyroxine sodium oral solution 175 and 200 µg/mL strengths.

2 Question-Based Review

2.1 Background

The sponsor seeks approval via the regulatory 505(b)(2) pathway for the 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 µg/mL strengths of levothyroxine sodium oral solution (LSOS) to treat hypothyroidism and pituitary thyrotropin-stimulating hormone suppression.

The same sponsor's Tirosint capsules (13, 25, 50, 75, 88, 100, 112, 125, 137, and 150 µg levothyroxine sodium) has the approved indications to treat hypothyroidism and pituitary thyrotropin-stimulating hormone suppression (NDAs 21-924 and 22-121 approvals on October 13, 2006 and August 1, 2007, respectively).

The sponsor originally developed a liquid formulation for oral use that consisted of a (b) (4) solution of levothyroxine ((b) (4) glycerol (b) (4) in squeezable low-density polyethylene containers. This formulation contains (b) (4) and it is intended for chronic administration in pediatric patients. Thus, the sponsor developed (b) (4) formulation relying on (b) (4) glycerol to (b) (4) levothyroxine.

The sponsor conducted the following 3 clinical pharmacology studies to support NDA 206-977:

- Study 130284 was a single-dose 3-way crossover study comparing the relative bioavailability of four 150 µg LSOS ampules (administered with 240 mL water or directly into the oral cavity without water) to four 150 µg Tirosint capsules in 36 fasting volunteers. Due to improper dispensing from the LSOS ampules (liquid remaining in ampules postdose), the assessment of relative bioavailability of the LSOS was invalid.
- Study 140143 was a pilot 3-way crossover study evaluating the rate and extent of absorption of 150 µg dosage strength LSOS ampules compared to 150 µg Tirosint capsules and 100 µg unit-dose ampules of the prototype (b) (4) formulation of LSOS, each administered as a 600 µg levothyroxine single oral dose.
- Study 140161 is the pivotal relative bioavailability study for LSOS. See Question 2.3.2 for details.

This reviewer did not review the following studies because:

- Study 130284 is a failed study.
- Study 140143 is a pilot relative bioavailability study.

This submission relies on 2 reference listed drugs (RLD), namely 150 µg Tirosint capsule for the 13 – 150 µg/mL LSOS and 300 µg Synthroid tablet for the 175 and 200 µg/mL LSOS. However, this submission does not contain a link between the 300 µg Synthroid tablet and the 175 µg/mL as well as 200 µg/mL LSOS. See the OPQ Biopharmaceutics review for justification of the 2 highest strengths of LSOS according to biowaiver requirements for the link between the 300 µg Synthroid tablet and 175 µg/mL as well as 200 µg/mL LSOS. The approved Tirosint capsule label contraindicates the use of Tirosint for infants and children or any child who may be unable to swallow a capsule. However, the approved Synthroid tablet label recommends that SYNTHROID may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5 – 10 mL or 12 teaspoons) of water.

The sponsor requested a biowaiver for the dosage-form proportionality study for the lower and higher strengths of LSOS in NDA 206-977. See the OPQ Biopharmaceutics review for justification the request

of biowaiver.

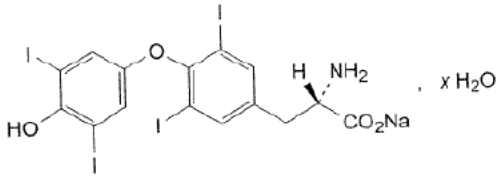
The Office of Study Integrity and Surveillance, Division of New Drug Bioequivalence Evaluation recommends accepting the data without an on-site inspection for the clinical and bioanalytical sites of Study 140161. See Shila Nkah's memorandum in DARRTS dated August 8, 2016.
The Pediatric Review Committee met on November 2, 2016 and agreed with the Division of Metabolism and Endocrinology Products' recommendation that no additional pediatric studies are necessary at this time because LSOS is properly labeled for use in all pediatric populations.

2.2 General Attributes

2.2.1 What are levothyroxine sodium's key physicochemical properties?

Levothyroxine sodium has a molecular weight of 798.85, empirical formula of $C_{15}H_{10}I_4NNaO_4$ (Figure 1), and is very slightly soluble in water. Levothyroxine sodium has pKa values of 2.2, 6.7, and 10.1 and has 1 chiral center. The L-form of thyroxine is the active pharmaceutical ingredient.

Figure 1. Levothyroxine sodium's molecular structure



where x = 5
Source: Submission's Section 3.2.S.1.2 Structure

2.2.2 What is the formulation for the to-be-marketed LSOS?

Table 1 shows the formulation of the to-be-marketed LSOS.

Table 1. The to-be-marketed LSOS.

Component Name	Quantity/unit	Function	Reference
Drug Substance			
Levothyroxine Sodium 13 µg 25 µg 50 µg 75 µg 88 µg 100 µg 112 µg 125 µg 137 µg 150 µg 175 µg 200 µg	 0.013 mg 0.025 mg 0.050 mg 0.075 mg 0.088 mg 0.100 mg 0.112 mg 0.125 mg 0.137 mg 0.150 mg 0.175 mg 0.200 mg	Active Ingredient	USP current edition
Excipient			
Glycerol (b) (4)	(b) (4)	(b) (4)	EP/USP current editions
Total			

*Corresponding to (b) (4) of glycerol (b) (4).
Source: Submission's Table 3.2.P.1.1

2.3 General Clinical Pharmacology

2.3.1 What are levothyroxine's clinical pharmacokinetic (PK) characteristics?

This reviewer extracted the following information from the approved Tirosint capsules label.

Absorption — Absorption of orally administered levothyroxine from the gastrointestinal tract ranges from 40 – 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. Levothyroxine absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybeans. Dietary fiber decreases the bioavailability of levothyroxine. Absorption may also decrease with age. In addition, many drugs and foods affect levothyroxine absorption.

Distribution — Plasma proteins bound more than 99% of circulating thyroid hormones. These proteins include thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for levothyroxine partially explains the higher serum concentrations, slower metabolic clearance, and longer half-life of levothyroxine compared to liothyronine. Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of unbound 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 — Elimination of levothyroxine is slow (see Table 2). The major metabolic pathway of thyroid hormone is through sequential deiodination. About 80% of circulating liothyronine comes from peripheral levothyroxine monodeiodination. The liver is the major site of degradation for both levothyroxine and liothyronine, with levothyroxine deiodination also occurring at a number of additional sites, including the kidney and other tissues. About 80% of the daily levothyroxine dose is deiodinated to yield equal amounts of liothyronine and reverse liothyronine. Liothyronine and reverse liothyronine are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized through conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Table 2. Pharmacokinetic parameters of thyroid hormones in euthyroid patients

Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{½}$ (days)	Protein Binding (%)
Levothyroxine (T_4)	10—20	1	6 – 7	99.96
Liothyronine (T_3)	1	4	≤ 2	99.5

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

2.3.2 What is the relative bioavailability under fasting between LSOS (150 µg/mL) taken with water and 150 µg Tirosint capsule as well as between LSOS (150 µg/mL) taken without water and 150 µg Tirosint capsule ?

Study 140161 was a randomized, open label, 3-way crossover relative bioavailability study in 36 male and female healthy volunteers (moderate smoker or non-smoker, aged ≥ 18 and ≤ 50 years, body mass index > 18.5 and < 30.0 kg/m^2, and body weight ≥ 50.0 kg for males and ≥ 45.0 kg for females).

After a supervised overnight fast (≥ 10 hours), each participant received either the test or reference medication according to the randomization scheme on September 12, 2014, October 17, 2014, and November 21, 2014 as a single dose of four 150 µg levothyroxine unit-dose ampules or four 150 µg Tirosint capsules. Participants received Treatments A and C with 240 mL of water and Treatment B without water. Participants subsequently fasted for a period of ≥ 4 hours postdose. Treatment coding:

- 1 (test): 4 x 150 µg LSOS unit-dose ampules administered with water

- 2 (test): 4 x 150 µg LSOS unit-dose ampules administered without water
- 3 (reference): 4 x 150 µg Tirosint capsules administered with water

Dosing Procedure for Treatment A (LSOS Administered With Water)

The content of the 4 unit-dose ampules of LSOS was diluted in 140 mL of room temperature water per the procedure described below. The solution was prepared immediately before dosing.

1. keeping a unit-dose ampule in vertical position (cap on top), it was opened cautiously by rotating the cap until complete detachment, without applying pressure on the ampule
2. holding the ampule between the 1st finger and thumb, it was inverted upside down in vertical position
3. the central, softer part of the ampule was squeezed slowly between the 1st finger and thumb to release the solution into a container (such as glass or cup) containing 140 mL of water
4. keeping the ampule in vertical position upside down, the pressure was released and a few seconds were waited
5. the procedure of ampule squeezing was repeated at least 5 times, until no more liquid leakage was seen
6. this empting procedure (steps 1 to 5) was repeated with each ampule
7. a minimal stirring of the oral solution in water was performed with a stick in the container before administration to participants.

The participant drank the solution from the container. The container was rinsed twice with 50 mL of water and the participant drank both of the 50 mL solutions. A minimal stirring of the rinsing solutions was performed with a stick in the container before administration to participants. The total amount of water consumed was 240 mL. The dosing procedure (including rinsing) must be completed within 3 minutes. The time of dosing was set to the time of administration of the 140 mL oral solution. For each participant, the 4 ampules were weighted altogether full and empty, prior to, and after dosing, respectively. The weights were recorded for indicative information.

Dosing Procedure for Treatment B (LSOS Administered Without Water)

The content of the 4 unit-dose ampules of oral solution were squeezed directly into the participant's mouth by study personnel through the following procedure:

1. keeping a unit-dose ampule in vertical position (cap on top), it was opened cautiously by rotating the cap until complete detachment, without applying pressure on the ampule;
2. holding the ampule between the 1st finger and thumb, it was inverted upside down in vertical position over the participant's mouth;
3. the central, softer part of the ampule was squeezed slowly between the first finger and thumb to release the solution directly into the participant's mouth;
4. keeping the ampule in vertical position upside down, the pressure was released and a few seconds were waited;
5. the procedure of ampule squeezing was repeated at least 5 times, until no more liquid leakage was seen;
6. this empting procedure (steps 1 to 5) was repeated with each ampule.

The dosing procedure must be completed within 3 minutes. The time of dosing was set to the time of administration of the 1st unit-dose ampule. For each participant, the 4 ampules were weighted altogether full and empty, prior to, and after dosing, respectively. The weights were recorded for indicative information.

Dosing Procedure for Treatment C (Tirosint Capsules)

Participants were allowed to swallow 1 or 2 capsules at a time until the 4 capsules were swallowed. The total amount of water consumed during the dosing procedure was 240 mL. The complete dose

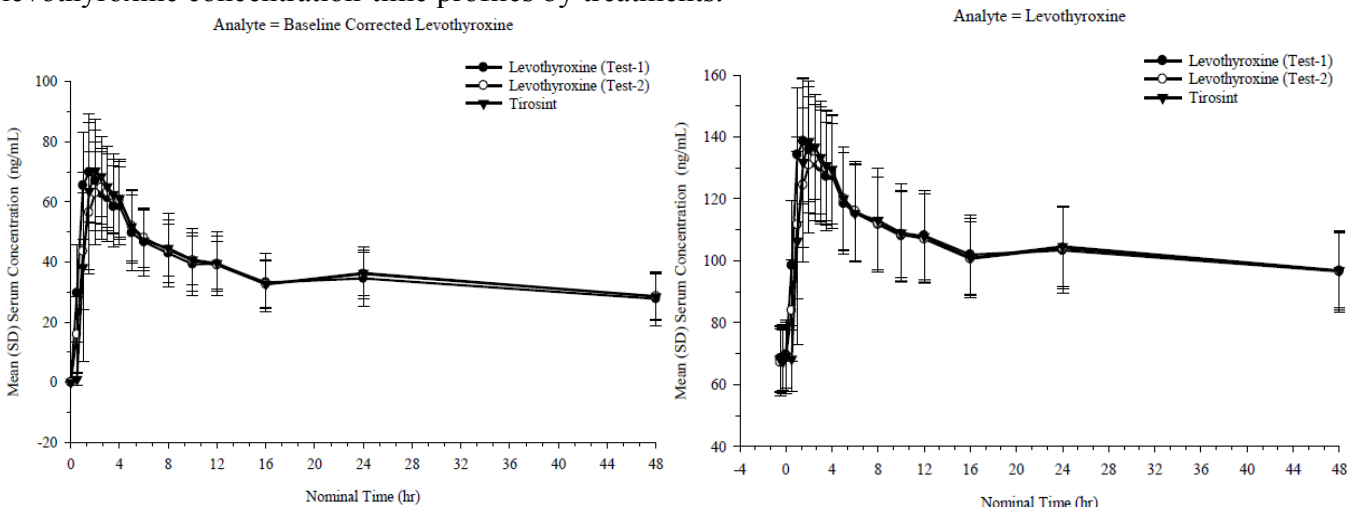
must be ingested within 2 minutes. The time of dosing was set to the time of administration of the 1st capsule. Participants were warned to neither chew nor bite the medication.

The sponsor used Batch 140701 to conduct Study 140161 and manufactured Batch 140701 according to the commercial manufacturing process. This process uses the commercial batch formulation. The bio-batch size (Batch 140701) is (b) (4) kg, whereas the production batch size is (b) (4) kg (submission Table 2.7.1-7). Thus, the bio-batch size for Study 140161 is acceptable. The sponsor studied the United States approved and marketed TIROSINT capsules in Study 140161 as the reference product. The Orange Book lists the 150 µg TIROSINT capsule as the RLD.

A washout of 35 days separated each treatment. The sponsor collected serial serum samples predose and 48 hours postdose. The sponsor measured levothyroxine concentration in the serum samples via a validated bioanalytical method.

The sponsor defined baseline levothyroxine value as the mean of the -0.500 hour, -0.250 hour, and within 5 minutes predose serum levothyroxine concentrations for each participant and treatment period. For baseline correction, the sponsor subtracted this baseline value (mean of the 3 predose samples) from each measured concentration, including the predose concentration, meaning that the predose concentration was equal to 0. If baseline-corrected postdose concentrations were negative, the sponsor set the concentrations to 0. Figure 2 shows the mean serum levothyroxine concentration-time graphs for the tests and reference as baseline corrected serum levothyroxine concentrations and baseline uncorrected serum levothyroxine concentrations.

Figure 2. Mean (SE) baseline corrected (left panel) and baseline uncorrected (right panel) of serum levothyroxine concentration-time profiles by treatments.



Source: Study 140161's report Figures 14.2.3-36 and 14.2.3-75

To verify the sponsor's relative bioavailability results, this reviewer used the PK parameters from the file "pklbc.xpt" and "pklbu.xpt" (submitted on June 1, 2016 via Serial 0004) for the baseline corrected and baseline uncorrected levothyroxine data, respectively. This reviewer used the SAS PROC GLM procedure (SAS version 9.4) to calculate the geometric mean ratio (GMR) and 90% confidence interval (CI) of levothyroxine AUC_{0-48} and C_{max}. This reviewer's 1st statistical analyses results are not consistent with the sponsor's analyses when this reviewer used the data for all participants. This reviewer also used the Phoenix software (version 64) to calculate the GMR and 90% CI of levothyroxine AUC_{0-48} and C_{max}. The Phoenix results are consistent with those of the SAS results. Tables 3 and 4 show the comparison of the results between this reviewer's 1st statistical analysis (with data from all participants) and the sponsor's results for baseline corrected levothyroxine PK parameters and baseline uncorrected

levothyroxine PK parameters, respectively .

Table 3. Statistical comparison of baseline corrected levothyroxine PK parameters between the reviewer's analysis with data from all participants and the sponsor's analysis.

				Reviewer's 1st analysis		Sponsor's Analysis	
Test	Reference	Parameter	unit	GMR	90% CI	GMR	90% CI
1	3	AUC_{0-48}	ng.hr/mL	98.47	90.56 – 107.07	98.47	94.97 – 102.11
1	3	C_{max}	ng/mL	95.33	91.99 – 98.79	95.33	91.97 – 98.82
2	3	AUC_{0-48}	ng.hr/mL	95.71	87.85 – 104.27	101.15	97.43 – 105.01
2	3	C_{max}	ng/mL	94.76	91.37 – 98.29	94.64	91.19 – 98.22
Treatment 1 = LSOS taken with water Treatment 2 = LSOS taken without water Treatment 3 = Tirosint Capsules							

Source: Reviewer's table.

Table 4. Statistical comparison of baseline uncorrected levothyroxine PK parameters between the reviewer's analysis with data from all participants and the sponsor's analysis.

				Reviewer's 1st analysis		Sponsor's Analysis	
Test	Reference	Parameter	unit	GMR	90% CI	GMR	90% CI
1	3	AUC_{0-48}	ng.hr/mL	99.93	91.54 – 109.1	99.94	98.33 – 101.58
1	3	C_{max}	ng/mL	97.7	95.58 – 99.85	97.7	95.57 – 99.87
2	3	AUC_{0-48}	ng.hr/mL	93.74	85.69 – 102.55	99.84	98.18 – 101.54
2	3	C_{max}	ng/mL	96.72	94.58 – 98.9	96.65	94.48 – 98.88
Treatment 1 = LSOS taken with water Treatment 2 = LSOS taken without water Treatment 3 = Tirosint Capsules							

Source: Reviewer's table.

Study 140161's report did not document that the statistical analysis did not include Participant 9's data. However, the study report's Tables 11.4.2.3-1 and Tables 11.4.2.3-4 have the fine print at the bottom that "Profile of Subject 9 was deleted." Thus, this reviewer did not include Participant 9's data in the 2nd statistical analysis.

This reviewer's 2nd statistical analysis is identical to the sponsor's statistical analysis. However, this reviewer's 1st statistical analysis may serve as a sensitivity analysis that included all participants' data. Exclusion of Participant 9's data for the relative bioavailability assessment in this 3-way crossover study is reasonable because Participant 9 did not finish Treatment 2 (Study 140161's report Figure 14.2.3-8).

For both the baseline corrected and baseline uncorrected levothyroxine PK parameters in this reviewer's 1st and 2nd statistical analyses:

- The 90% CI of levothyroxine AUC_{0-48} GMR and levothyroxine C_{max} GMR show that the levothyroxine in the 150 µg/mL strength of LSOS taken with 240 mL of water is bioequivalent to the levothyroxine in 150 µg of Tirosint capsule under fasting condition because the 90% CIs are within the 80 and 125% bioequivalence goalpost.
- The 90% CI of levothyroxine AUC_{0-48} GMR and levothyroxine C_{max} GMR show that the levothyroxine in the 150 µg/mL strength of LSOS taken without water is bioequivalent to the levothyroxine in 150 µg of Tirosint capsule under fasting condition because the 90% CIs are within the 80 and 125% bioequivalence goalpost.

2.4 Bioanalytical

Is the bioanalytical method properly validated to measure levothyroxine in serum samples?

The sponsor extracted levothyroxine from aliquots of serum samples via a solid phase extraction procedure and then injected the extracts into a liquid chromatography with tandem mass spectrometry (LC/MS/MS) system to measure the levothyroxine concentrations. Table 5 summarizes the validation data of levothyroxine for Study 140161.

Table 5 Validation of the bioanalytical assay to measure levothyroxine in serum samples for Study 140161.

	Levothyroxine
Matrix	serum
Sample volume, mL	0.05
LOQ, ng/mL	25
Linear range, ng/mL	25 – 250
QC concentrations, ng/mL	58.39, 83.44, 118.51, and 183.64
Assay QC Precision (% CV)	
Interrun-	3.71 – 10.58
Intrarun-	1.14 – 2.48
Accuracy QC (%)	
Interrun-	-0.63 – 2.33
Intrarun-	-2.06 – 1.73
Average drug recovery, %	43.32, 57.48, and 57.97
Average IS recovery, %	63.51
Bench top stability, hours	22.75 at room temperature
Stock stability, days	429 at -20°C
Process stability, hours	98.75 at room temperatures
Freeze-thaw stability, cycles	4 at -20°C
Long-term storage stability, days	350 at -20°C
Dilution integrity, ng/mL	DQC diluted 1/20: 5049.29 % CV = 4.74% % Bias = 3.54%
Selectivity	No interfering peak noted in blank plasma samples for levothyroxine and IS

LOQ = limit of quantitation; QC = quality control; IS = internal standard = thyroxine $^{13}C_6$; DQC = dilution quality control
Source: This reviewer's modified version of the sponsor's submission, Bioanalytical Report for Study 140161/14CDN/T403.

Validations for the LC/MS/MS bioanalytical method to measure levothyroxine in serum samples for Study 140161 appear acceptable with reasonable precision and accuracy.

3. Labeling Recommendations

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immeidately following this page

4 Appendix

4.1 Individual Study Synopsis

2. Study Synopsis

Study 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	
Project No.:	140161 (Sponsor Project Number: 14CDN/T403)
Qualified Investigator:	Josée Villeneuve, M.D.
Study Centre: Clinical (b) (4)	inVentiv Health Clinique inc. 2500, rue Einstein Québec (Québec) Canada, G1P 0A2 Tel.: 418-527-4000 Fax: 418-527-3456
Dates of the Clinical Portion:	First dosing: 12-SEP-2014 Last dosing: 21-NOV-2014 Scheduled study exit procedures: 21-DEC-2014 Last subject last visit: 04-FEB-2014
Study Phase:	Clinical Phase I (Comparative Bioavailability [BA])

Objective:

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

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

Study Design:

This was a single centre, randomized, single-dose, open-label, 3-way crossover comparative BA study to compare the rate and extent of absorption of a test levothyroxine sodium oral solution versus Tirosint® capsules, a reference levothyroxine sodium product approved for sale in United States, and to compare the rate and extent of absorption of a test levothyroxine sodium oral solution administered with or without water, under fasting conditions. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme generated by inVentiv. Subjects were confined to the inVentiv Clinical Facility from at least 10 hours prior to drug administration until after the 48.0-hour post-dose

blood draw, in each period. Subjects were asked to come back to the clinical facility for a safety visit one month following the last dose of levothyroxine. The treatment phases were separated by a washout period of 35 days.

Subjects:

Randomized and dosed: 36 (18 females and 18 males)

Withdrew consent of at least one period: 4

Withdrawal: 1

Completed: 31

Safety population: 36

Pharmacokinetic (PK) population: 34 (for comparison A/C) and 32 (for comparison B/A)

Diagnosis and Main Criteria for Inclusion:

Subjects had to be healthy, adult subjects, moderate smoker or non-smoker, aged ≥18 and ≤50 years; body mass index (BMI) >18.5 and <30.0 kg/m^2 and body weight ≥50.0 kg for males and ≥45.0 kg for females. Screening procedures included informed consent, inclusion/exclusion criteria, medical and medication histories, demographic data, body measurements, vital signs measurements, 12-lead electrocardiogram (ECG), physical examinations, urine drug screen, urine pregnancy test (female subjects), and clinical laboratory tests (hematology, biochemistry, endocrinology, serology, and urinalysis). All subjects were in compliance with the inclusion and exclusion criteria described in the protocol and were judged eligible for enrolment in this study.

Treatment		
Treatment Identification:	**Test (A and B)**	**Reference (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:	[redacted] (b) (4)	
Strength:	150 µg	150 µg
Dosage Form:	Oral solution, unit-dose ampule	Capsule
Dose Administered:	4 x 150 µg	4 x 150 µg
Potency:	99.6%	99.4%
Route of Administration:	Oral	Oral

Duration of Treatment:

A single oral dose of 600 µg levothyroxine as 4 x 150 µg unit-dose ampules of oral solution or 4 x 150 µg capsules were administered in each study period. The treatment phases were separated by washout periods of 35 days.

Blood Sampling Points:

Blood samples were collected prior to study drug administration and -0.500 hour, -0.250 hour and within five minutes (0 hour) prior to drug administration, 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 hour post-dose in each period.

Criteria for Evaluation:

Pharmacokinetics:

AUC_{0-48}, C_{max}, and T_{max}.

Safety:

Adverse events (AEs), vital signs, ECGs, physical examination, and standard clinical laboratory evaluations.

Statistical Methods:

Pharmacokinetics:

- Parametric ANOVA on AUC_{0-48}, C_{max}, and T_{max}; geometric confidence intervals for AUC_{0-48} and C_{max};
- Factors in the ANOVA model: sequence, subject within sequence, period, and treatment;
- Ln-transformed parameters: AUC_{0-48} and C_{max}.

Criteria for bioequivalence for baseline corrected total (bound and free) levothyroxine (T4):

- 90% geometric confidence intervals of the ratio (A/C) of least-squares means from the ANOVA of the ln-transformed AUC_{0-48} and C_{max} must be within 80.00% to 125.00%.

Uncorrected and baseline corrected data are presented for total levothyroxine. Results without baseline correction are provided for information purposes.

Safety:

Descriptive only for AEs.

Results:

Pharmacokinetics:

Table I: Baseline Corrected Levothyroxine – Summary of Pharmacokinetic Results for Each Treatment

	Serum Baseline Corrected Levothyroxine		
	Levothyroxine (Test-1)	Levothyroxine (Test-2)	Tirosint
N	35	32	34
AUC_{0-48}[a] (ng•hr/mL)	1739.26 ± 438.25 (25.20)	1755.86 ± 330.86 (18.84)	1764.14 ± 380.88 (21.59)
C_{max}[a] (ng/mL)	72.66 ± 16.67 (22.95)	71.30 ± 14.19 (19.91)	76.64 ± 16.48 (21.51)
T_{max}[b] (hr)	1.50 (1.00 - 4.00)	2.50 (1.00 - 5.00)	2.00 (1.00 - 4.00)

[a]Mean ± SD
(CV%)

[b] Median
(Min - Max)

Profile of Subject 9 was excluded

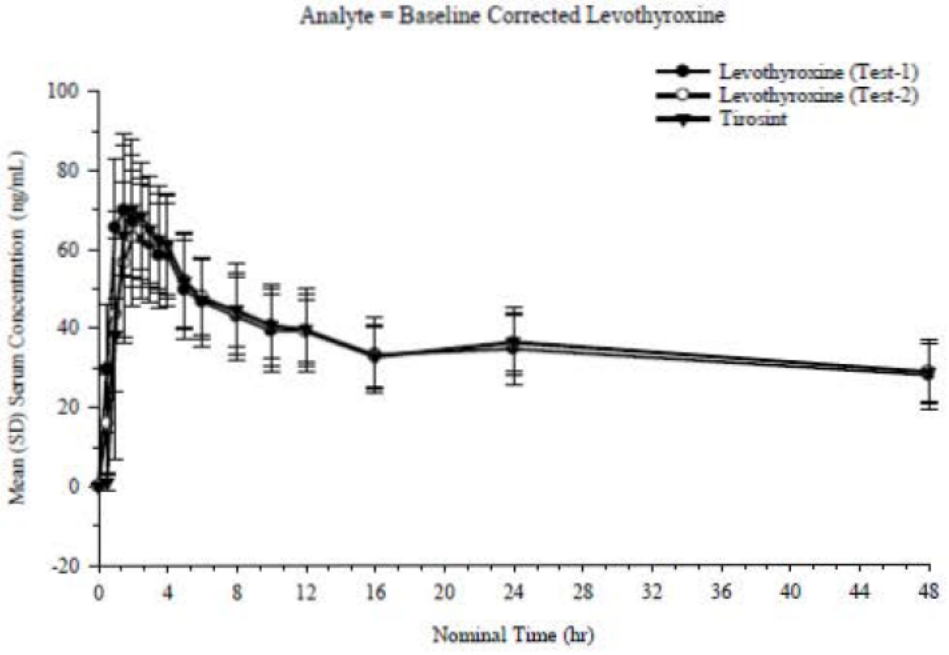
Table II: Baseline Corrected Levothyroxine – Ratios and Confidence Intervals

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2] Lower	Upper	Intra-Subject CV	Inter-Subject CV
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: $e^{(DIFFERENCE)} \times 100$.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Figure I: Mean Baseline Corrected Levothyroxine Serum Concentrations vs Time Profiles

a) Linear-Scale



b) Log-Scale

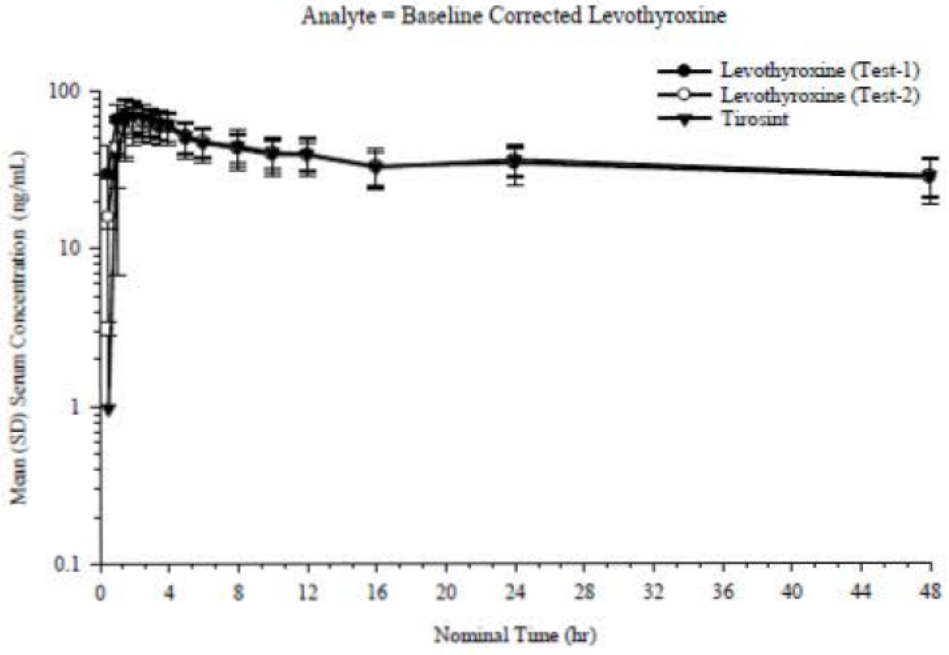


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Table III: Levothyroxine –
Summary of Pharmacokinetic Results for Each Treatment

Serum Levothyroxine

	Levothyroxine (Test-1)	Levothyroxine (Test-2)	Tirosint
N	35	32	34
AUC_{0-48}[a] (ng•hr/mL)	5044.06 ± 653.79 (12.96)	5025.27 ± 618.99 (12.32)	5043.75 ± 623.59 (12.36)
C_{max}[a] (ng/mL)	141.48 ± 20.30 (14.35)	139.38 ± 18.97 (13.61)	144.96 ± 19.45 (13.42)
T_{max}[b] (hr)	1.50 (1.00 - 4.00)	2.50 (1.00 - 5.00)	2.00 (1.00 - 4.00)

[a] Mean ± SD
(CV%)

[b] Median
(Min - Max)

Profile of Subject 9 was excluded

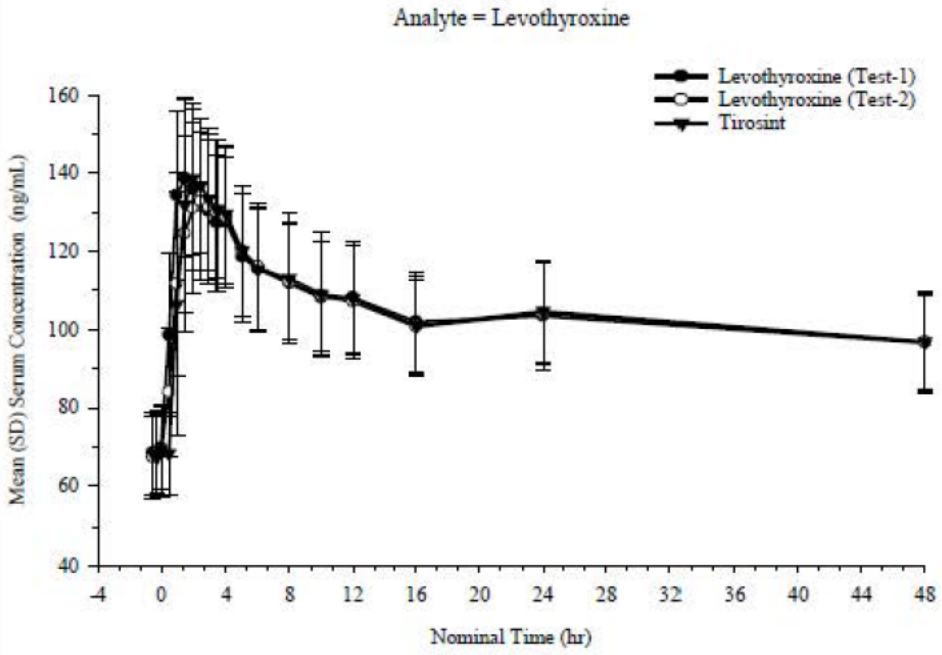
Table IV: Levothyroxine – Ratios and Confidence Intervals

Parameter	Treatment Comparisons	Ratio[1]	90% Geometric C.I.[2] Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-48}	Test-1(A) - Reference(C)	99.94%	98.33%	101.58%	4.03%	13.10%
	Test-2(B) - Test-1(A)	99.90%	98.25%	101.58%		
C_{max}	Test-1(A) - Reference(C)	97.70%	95.57%	99.87%	5.46%	14.12%
	Test-2(B) - Test-1(A)	98.93%	96.73%	101.19%		

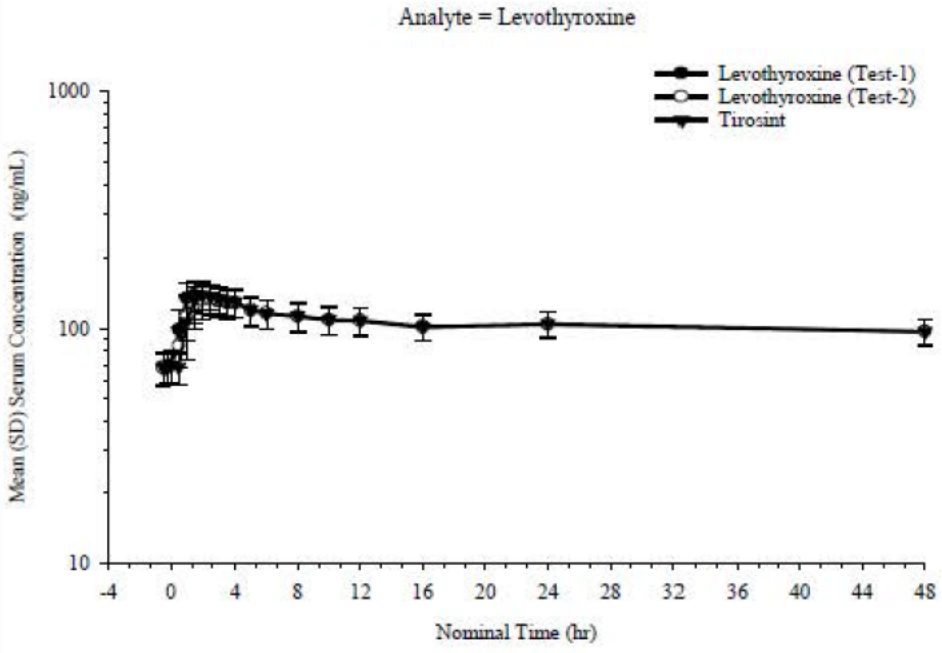
[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)} \times 100$.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Figure II: Levothyroxine Serum Concentrations vs Time Profiles

a) Linear-Scale



b) Log-Scale



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Safety:

A total of 47 treatment-emergent AEs (TEAEs) were reported by 24 of the 36 subjects who received at least one dose of the study medication (safety population). The majority of TEAEs were of mild severity and resolved spontaneously without any countermeasure. Twenty-six (26) of the 47 TEAEs reported were judged as possibly related to the study treatment. The fact that no severe TEAEs and no SAEs were reported in this study indicates that the study formulations were well tolerated, with no major side effects.

No deaths or other SAEs were reported during this study. One subject experienced the significant TEAE "Sinusitis" and one subject experienced the significant TEAE "Alanine aminotransferase increased". The subjects' safety was not at risk during the study. The safety evaluation performed on subjects completing study exit procedures (including clinical laboratory tests, vital signs measurements, and ECGs), confirmed the absence of significant changes in the subject's state of health.

Conclusions:

Safety:

All formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed among the preparations.

Pharmacokinetics:

Based on the baseline corrected levothyroxine results, it can be concluded that the Test 1 (Levothyroxine sodium oral solution 150 µg unit-dose ampules - Treatment A) is bioequivalent to the Reference Tirosint (Levothyroxine sodium 150 µg capsule - Treatment C) following a 4 x 150 µg dose (total dose of 600 µg) administered with water under fasting conditions.

In addition, it can be concluded that the rate and extent of absorption of the Levothyroxine sodium oral solution 150 µg unit-dose ampules formulation administered without water is comparable to its administration with water following a 4 x 150 µg dose (total dose of 600 µg) under fasting conditions.

Results without baseline correction are presented for supportive information only and are therefore not discussed in the conclusions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SZE W LAU
11/06/2016

JAYABHARATHI VAIDYANATHAN
11/07/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	206-977	**SDN**	1
Applicant	IBSA Institut Biochimique SA	**Submission Date**	February 26, 2016
Generic Name	Levothyroxine sodium	**Brand Name**	Tirosint-SOL
Drug Class	Thyroid hormone		
Indication	Treat hypothyroidism and pituitary thyrotropin-stimulating hormone (TSH) suppression; use in patients < 6 years of age		
Dosage Regimen	Individualized		
Dosage Form	Solution	**Route of Administration**	Oral
OCP Division	2	**OND Division**	DMEP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	S.W. Johnny Lau	Jayabharathi Vaidyanathan
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	4/26/2016	**74-Day Letter Date**	5/10/2016
Review Due Date	10/24/2016	**PDUFA Goal Date**	12/23/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes See the "Reasons for Filing NDA 206-977" section at the end of this review.

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s)

See the "Information Request through the 74-Day Letter" section at the end of this review.

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain: Bioequivalent study (140161-14CDN/T403) is the pivotal clinical study for this entire NDA submission.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		3	Studies 130284/13CDN/T406 (incomplete dosing), 140143/14CDN/T405 (pilot), and 140161/14CDN/T403 (pivotal)
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	3	Studies 130284/13CDN/T406 (incomplete dosing), 140143/14CDN/T405 (pilot), and 140161/14CDN/T403 (pivotal)
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	3
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)

RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	The biobatch 140701 is the commercial formulation.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	Pivotal Study 140161/14CDN/T403 and biowaiver request
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	Pivotal Study 140161/14CDN/T403
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	Datasets and bioanalytical reports are available for Studies 140143/14CDN/T405 and 140161/14CDN/T403. Study reports are available for Studies 130284/13CDN/T406, 140143/14CDN/T405, and 140161/14CDN/T403.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		

Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

The sponsor conducted the following 3 clinical pharmacology studies to support NDA 206-977:

- 130284-13CDN/T406
- 140143-14CDN/T405
- 140161-14CDN/T403

Study 130284-13CDN/T406 is invalidated [redacted] (b) (4).
Study 140143-14CDN/T405 is the pilot bioequivalence study. Study 140161-14CDN/T403 is the pivotal bioequivalence study. The sponsor used Batch 140701 to conduct Study 140161-14CDN/T403 and manufactured Batch 140701 according to the commercial manufacturing process. This process uses the commercial batch formulation. See Module 2.7.1.1.4, Module 3.2.P.3.3, and Table 3.2.P.3.2.1.

Reasons for Filing NDA 206-977

- Clinically-tested formulation is the same as the to-be-marketed formulation.
- Provided human bioequivalence data to link the 150 µg/mL levothyroxine sodium oral solution (LSOS) and the 150 µg Tirosint capsule (reference listed drug; RLD).
- Provided biowaiver request for a dosage-form proportionality study for the lower and higher strengths of LSOS.
- This submission is a 505(b)(2) application and relies on 2 RLDs, namely 150 µg Tirosint capsule for the 13 – 150 µg/mL LSOS and 300 µg Synthroid for the 175 and 200 µg/mL LSOS. However, this submission does not contain a link between the 300 µg Synthroid tablet and the 175 µg/mL as well as 200 µg/mL LSOS. OPQ Biopharmaceutics will be responsible for the review of justification for the 2 highest strengths according to biowaiver requirements for the link between the 300 µg Synthroid tablet and 175 µg/mL as well as 200 µg/mL LSOS for filing because of:
  - the biowaiver request as recommended by DMEP's July 3, 2013 letter
  - subsequent email exchanges between the sponsor and DMEP from September 25, 2013 to September 29, 2013
- Provided bioanalytical and validation reports as well as electronic datasets for Studies 403 and 405.
- Annotated proposed label of LSOS for review.

Information Request through the 74-Day Letter

Are the 0.15 mg Tirosint capsules tested in Study 140161-14CDN/T403 approved and marketed in the United States?

Study 140161-14CDN/T403's report provided the bioequivalence assessment between levothyroxine sodium oral solution (LSOS) with water and Tirosint capsule for the baseline-corrected levothyroxine pharmacokinetic parameters. The sponsor needs to provide the following for Study 140161-14CDN/T403:

- The bioequivalence assessment between LSOS without water and Tirosint capsule for the baseline-corrected levothyroxine PK parameters.
- The bioequivalence assessment for the baseline-uncorrected levothyroxine pharmacokinetic parameters for the following:
  - between LSOS with water and Tirosint capsule
  - between LSOS without water and Tirosint capsule

- between LSOS without water and LSOS with water

Need for Clinical Trial Inspection

Study 140161-14CDN/T403's Clinical site:
Principal Investigator:
Josée Villeneuve, M.D.
inventive Health Clinique inc.
2500, rue Einstein
Québec (Québec)
Canada, G1P 0A2
Tel.: (418) 527-4000
Fax: (418) 527-3456

Study 140161-14CDN/T403's (b) (4)

22 Page(s) have been Withheld in Full immediately following this page as a duplicate copy of the meeting minutes dated 7/3/13 on epg 49 and also an email dated 9/29/13 with attached FDA slides filed in the Administrative and Correspondence section of this approved NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SZE W LAU
04/18/2016

JAYABHARATHI VAIDYANATHAN
04/19/2016