# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-924**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: | 21-924 |
| Submission Date(s): | December 07, 2005; March 30, 2006; June 27, 2006 |
| Brand Name: | Tirosint™ |
| Generic Name: | Levothyroxine Sodium Soft Capsules |
| Reviewer: | Sang M. Chung, Ph.D. |
| Team Leader: | Hae-Young Ahn, Ph.D. |
| OCP Division: | DCP 2 |
| ORM division: | DMEP |
| Sponsor: | Institut Biochimique SA (IBSA) |
| Relevant IND: | 70,039 |
| Submission Type: | Original NDA, 505(b)(2) |
| Formulation: | Soft Capsule; 12.5, 25, 50, 75, 100, 125 & 150 µg |
| Indication: | Hypothyroidism / Pituitary TSH Suppression |

## Table of Contents

**Lists of Figures and Tables**

# 1 Executive Summary

## 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 21-924 and finds it acceptable. The Recommendation should be sent to the sponsor as appropriate.

## 1.2 Phase IV Commitments

N/A

## 1.3 Summary of Clinical Pharmacology Findings

Relative bioavailability of Tirosint™ to Synthroid® was evaluated in a two-way crossover study. The pharmacokinetics of levothyroxine after Tirosint™ administration were comparable to those following Synthroid® administration, and it was concluded that Tirosint™ is bioequivalent to Synthroid® (Table 1).

**Table 1 Statistical analysis for the BE assessment**

| Parameter | Ratio (%) (Test/Reference) | 90% Confidence interval |
|---|---|---|
| $AUC_{0-t}$ (n=24; adjusted with the baseline) | **103.0** | **92.8-114.4** |
| $C_{max}$ (n=24; adjusted with the baseline) | **106.8** | **100.7-113.2** |

In addition, the dosage form equivalence was evaluated in a single dose (600µg), three-way crossover study using 50, 100, and 150µg strengths, and it was concluded that dosage forms were equivalent.

# 2 Question-Based Review (QBR)

## 2.1 General Pharmacology

2.1.1 What were the rationales for developing a soft capsule formulation?

The sponsor proposed 5 rationales as follows:

1. A lot-to-lot and/or unit-to-unit variability was a significant issue with tablets because distribution uniformity of levothyroxine throughout each dosage unit was difficult to achieve. However, the soft capsules were to use solution and the distribution uniformity was relatively not an issue in solution.
2. The soft capsules had outer shell and it provided extra protection against light, air, and humidity, which were known to have deleterious influence on levothyroxine stability.
3. The tableting processes were known to generate high compression temperature up to 200°C and it could be deleterious influence on levothyroxine stability. The soft capsule manufacturing processes were not exposed to temperature beyond 40°C.
4. The soft capsules were easier to swallow than tablets.
5. The soft capsule manufacturing processes were less harmful to manufacturing technicians since there were no mixing/compounding in a dry powdery state compared to those of tablets.

2.1.2 What were the results of a BE study?

Bioequivalence of Tirosint™ (Lot No.: 040705) to Synthroid® (Lot No.: 0000348181) was assessed in a randomized, single dose, two-way crossover study following oral administration of a 600µg total dose to healthy volunteers under fasting conditions (Study AA05227). There was 35 days washout period between treatments. A total of 25 subjects completed the study (female=13, males = 12).

Baseline value was calculated from three serum levothyroxine levels before the treatment (i.e., 30, 15, and 5 minutes before the treatment). Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours after dosing. Serum levothyroxine levels were measured using RIA method.

Bioequivalence was assessed based on the following formula and ANOVA on the ln-transformed baseline-adjusted pharmacokinetic parameters:

$$\text{Ratio of least-square means: } 100 \times e^{(LSM_t - LSM_r)}$$

$$\text{90\% confidence interval: } 100 \times e^{(LSM_t - LSM_r \pm t_{df,0.05} \times SE_{t-r})}$$

$$\text{Intrasubject CV\%: } 100 \times \sqrt{e^{MSE} - 1}$$

where,

- $t_{df,0.05}$ was the value of the Student's *t*-distribution with degrees of freedom for the error term from the analysis of variance, and a right-tail fractional area
- $LSM_t$ and $LSM_r$ were the least-squares means of the test and reference formulations, respectively, as computed by the LSMEANS statement of the SAS® GLM procedure.
- MSE was the mean square error from the analysis of variance

- $SE_{t-r}$ was the standard error of the difference between the adjusted formulation means, as computed by the ESTIMATE statement in the SAS® GLM procedure

Serum concentration-time profiles after the treatments were shown in the Figure 1.

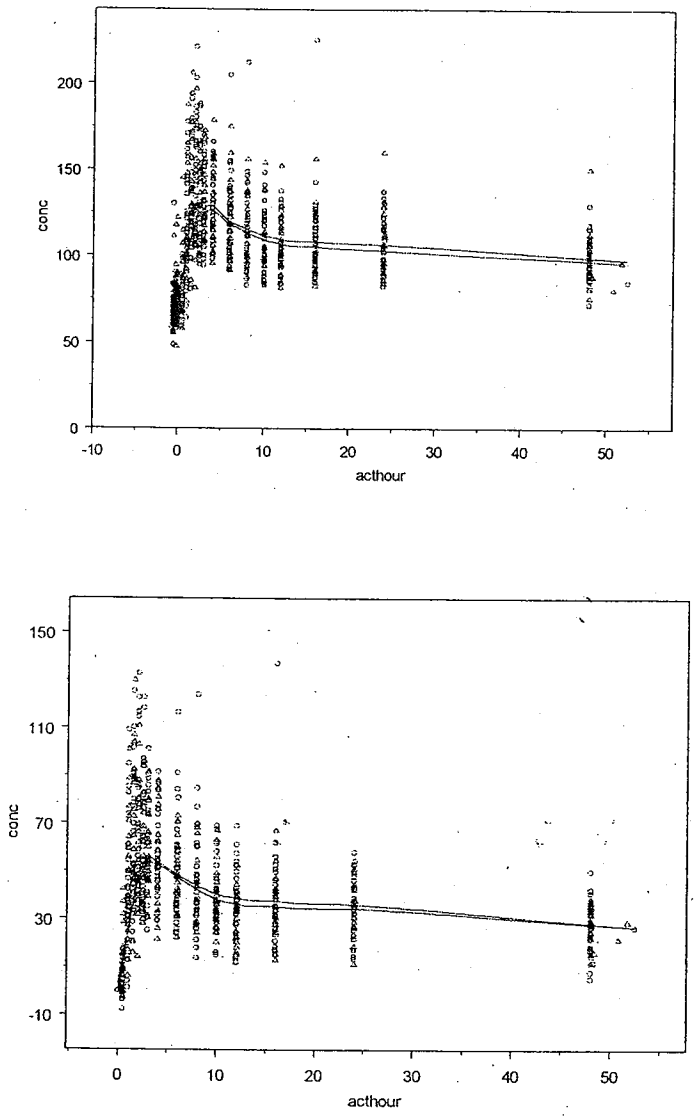


**Figure 1** **Serum concentration-time profiles of levothyroxine after Tirosint™ (open circle) and Synthroid® (open triangle): unadjusted (upper panel) and baseline adjusted (lower panel). Lines are based on Loess fit.**

There was no apparent period effect on the baseline as shown in the Table 2.

**Table 2** **Serum levothyroxine concentrations before dosing; Arithmetic mean (SD)**

| | Period* | |
|---|---|---|
| **Sampling Time (hr)** | **1** | **2** |
| -0.5 | 69.19 (8.097) | 71.77 (17.36) |
| -0.25 | 71.21 (9.54) | 71.63 (13.75) |
| -0.083 | 71.54 (8.49) | 72.57 (13.84) |

*: N=24 except period 2 at -0.5 hr (n=23).

Pharmacokinetic parameters after the treatments were summarized in the following table.

**Table 3** **Summary of levothyroxine pharmacokinetic parameters (arithmetic mean and SD)**

| | Adjusted | | Unadjusted | |
|---|---|---|---|---|
| **Parameter** | **Test** (Tirosint™) | **Reference** (Synthroid®) | **Test** (Tirosint™) | **Reference** (Synthroid®) |
| $AUC_{0-t}$ (ng h/ml; n=24) | 1812.7 (621.68) | 1709.9 (435.15) | 5246.2 (730.58) | 5163.7 (788.73) |
| $C_{max}$ (ng/ml; n=24) | 80.41 (29.181) | 73.69 (21.918) | 151.56 (32.101) | 145.12 (26.589) |
| Tmax (h; n=24) | 2.9 (2.95) | 2.1 (0.83) | 3.4 (2.95) | 2.6 (0.83) |

Results of the statistical analysis showed that Tirosint™ was BE to Synthroid® based on the baseline adjusted concentrations (Table 1).

2.1.3 What were the results of dosage form equivalence study?

The dosage form equivalence was evaluated in a randomized, single-dose, three-way crossover study following oral administration of a 600µg total dose to healthy volunteers under fasting conditions (Study AA05228). Single oral doses of the 600µg doses using three strengths (i.e., 12 capsules of 50µg, 6 capsules of 100µg, and 4 capsules of 150µg) were administered in the study and the treatments were separated by at least 35 days washout period. Study methods were the same as those in the BE study. Primary levothyroxine pharmacokinetic parameters were summarized in the following table.

**Table 4** **Summary of levothyroxine pharmacokinetic parameters (arithmetic mean and SD)**

| | Adjusted | | | Unadjusted | | |
|---|---|---|---|---|---|---|
| **Parameter** | **50µg** | **100µg** | **150µg** | **50µg** | **100µg** | **150µg** |
| $AUC_{0-t}$ (ng h/ml; n=24) | 1795.0 (510.62) | 1854.7 (570.06) | 1830.0 (567.18) | 5611.9 (621.70) | 5727.0 (711.17) | 5576.6 (849.32) |
| $C_{max}$ (ng/ml; n=24) | 75.0 (20.77) | 80.0 (27.30) | 80.9 (22.79) | 154.2 (22.69) | 160.3 (30.29) | 160.6 (24.49) |
| Tmax (h; n=24) | 2.5 (1.50) | 2.2 (0.79) | 2.0 (0.84) | 3.0 (1.50) | 2.7 (0.79) | 2.6 (0.84) |

The dosage form equivalence was evaluated using statistical analysis for BE assessment and dosage form equivalence was concluded based on least-square mean ratios and 90% confidence intervals of the baseline-adjusted levothyroxine pharmacokinetic parameters. Results of statistic analysis were summarized in the following table. The study has demonstrated that the 50µg, 100µg, and 150µg are dosage form equivalent.

**Table 5** **Results of BE assessment using the baseline-adjusted serum levothyroxine concentrations**

| | Ratio (90% CI) | |
|---|---|---|
| **Parameter** | **50µg vs. 100µg** | **150µg vs. 100µg** |
| $AUC_{0-t}$ (ng h/ml; n=24) | 97.3% (89.1-106.3) | 98.8 (90.4-107.9) |
| $C_{max}$ (ng/ml; n=24) | 95.6 (87.8-104.0) | 103.0 (94.6-112.1) |

The clinical study site and analytical site were as follows:

Clinical study site: [redacted]

Analytical study site was at [redacted], and pharmacokinetic analyses were performed at [redacted]. The clinical study and analytical study site were inspected by DSI in 2003-2004 related to Levo-T (NDA 21-342 S-003), and thus DSI inspection was not requested.

## 2.2 General Biopharmaceutics

2.2.1 What were the components of the to-be-marketed formulation?

The drug substance was solubilized in [redacted], and then the solution was injected into the space between two gelatin ribbons during the encapsulation process. The qualitative and quantitative compositions of each strength were summarized in the following table.

# 1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-1*

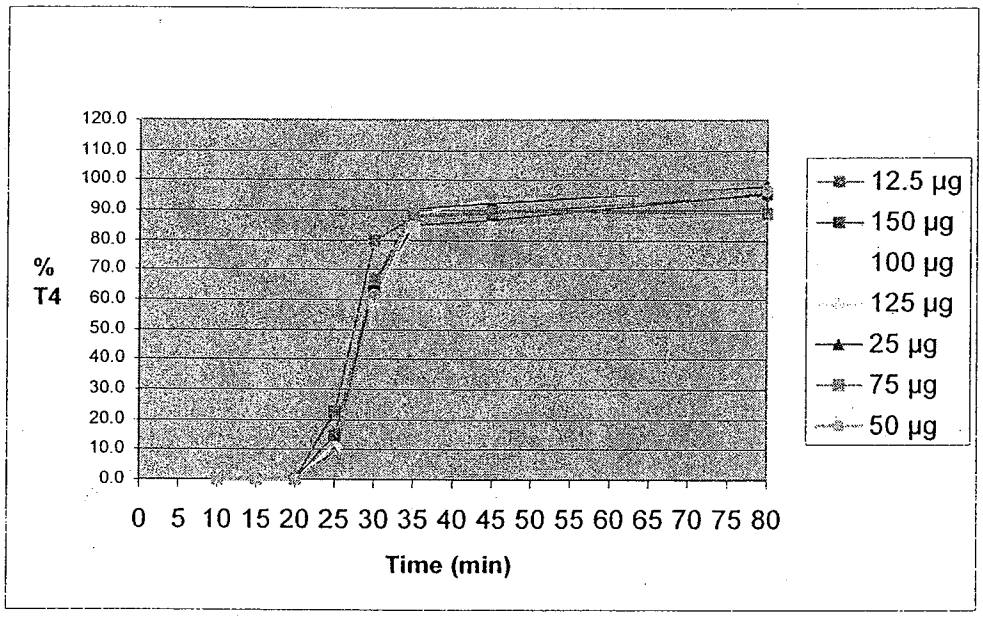


**Figure 3** **Mean (three batches) dissolution profiles**

The proposed specification was not less than [redacted] at 45 minute and it was acceptable.

2.2.3 Was the biowaver request acceptable?

Dissolution profiles were compared for biowaiver using a similarity factor (f2) based on recommendations in Guidance for Industry, Dissolution testing of immediate release solid oral dosage forms, and the results indicated that dissolution profiles were the same across strengths (Table 7). Samples at 10, 15, 20, 30, and 35 minute were included in the similarity factor calculation. The levothyroxine release in the dissolution condition was with about 20 minute lag time and it seemed that sampling at 10, 15, and 20 minutes ensured quality control of gel capsule rupture. It was concluded that the biowaiver requests for [redacted], 25, 75, and 125µg were acceptable.

**Table 7** **Summary of the similarity factor (f2)**

| | 50µg vs. 25µg | 50µg vs. 12.5µg | 100µg vs. 75µg | 150µg vs. 125µg* |
|---|---|---|---|---|
| f2 | 87.89 | 54.52 | 73.37 | 79.30 |

*: sampling of at 45 minute was included since it fulfilled the rules in the above mentioned Guidance.

## 2.3 Analytical

### 2.3.1 Was bioanalytical method acceptable?

Serum concentrations of levothyroxine were measured using standard radioimmunoassay. The report on bioanalytical method validation for the Study AA05227 was summarized in the following table, and the method was acceptable based on the results.

**Table 8 Results of bioanalytical method validation**

| | |
|---|---|
| Limit of quantitation (ng/ml) | 16.025 |
| Standard curve concentrations (ng/ml) | 10.015-300.462 |
| QC concentrations (ng/ml) | 30.045, 100.559, 2 |
| QC intraday precision range (%) | 2.6-6.3 |
| QC interday precision range (%) | 0.6-6.3 |
| QC interday accuracy range (%) | 96.2-109.2 |

## 3 Labeling Comments

None

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8/30/2006 11:10:11 AM
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# *Office of Clinical Pharmacology and Biopharmaceutics*
# *New Drug Application Filing and Review Form*

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| NDA Number | 21-924 | Brand Name | Tirosint |
| OCPB Division (I, II, III, IV, V) | DCPB II | Generic Name | Levothyroxine sodium soft capsule |
| Medical Division | DMEP | Drug Class | A thyroid hormone drug product |
| OCPB Reviewer | Sang M. Chung, Ph.D. | Indication(s) | Hypothyrodism<br>Pituitary TSH suppression |
| OCPB Pharmacometrics Reviewer | None | Dosage Form | Tablet; 12.5, 25, 50, 75, 100, 125 and 150 mcg |
| OCPB Team Leader | Hae-Young Ahn, Ph.D. | Dosing Regimen | |
| Date of Submission | 11/30/2005 | Route of Administration | Oral |
| Estimated Due Date of OCPB Review | | Sponsor | Institute Biochimique SA (IBSA) |
| PDUFA Due Date | | Priority Classification | |
| Division Due Date | | | |

**Clin. Pharm. and Biopharm. Information**

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| ***Healthy Volunteers-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| ***Patients-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |

| | | | | |
|---|---|---|---|---|
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | X | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | X | 2 | | |
| traditional design; single / multi dose: | X | 2 | | 1: BE to Synthroid<br>2: Dosage form equivalence |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | 2 | | | |

| Filability | | |
|---|---|---|
| | "X" if yes | Comments |
| **Application filable ?** | X | Levothyroxine dissolution profiles were not consistent among capsules in the same batch and strength, and thus the results were not acceptable. Therefore, it is recommended that the sponsor develop a dissolution method with consistent levothyroxine release from the soft gel capsule. USP Apparatus I (basket) is known to be suitable for soft gel dissolution study. [redacted]<br><br>Justification on the selection of dissolution medium should be submitted. For example, at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) should be tested (refer Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations).<br><br>Graphical summary of dissolution study results should be submitted.<br><br>In general, DSI inspection for the clinical study and analytical study is recommended for the pivotal BE studies especially in 505(b)(2) application. However, the clinical study and analytical study site were inspected by DSI in 2003-2004 related to Levo-T (NDA 21-342 S-003). Therefore, DSI inspection will not be requested unless there is any other regulatory concern. |
| **Submission in brief** | | The sponsor developed a soft gel capsule for levothyroxine and advocated that the new formulation significantly improved stability and lot-to-lot variability of levothyroxine. This submission is a 505(b)(2) application referencing data from Synthroid® manufactured by Abbott Laboratories.<br><br>The capsule consisted of [redacted] gelatin [redacted], gelatin [redacted] water [redacted], and levothyroxine.<br><br>Two *in vivo* comparative bioavailability studies were conducted for the application. One was the BE study (Study AA05227, n=25) between the test product and Synthroid® following 600mcg dose (four capsules of 150mcg for the test product and four tablets of 150mcg for Synthroid®). The other was the dosage form equivalence study (Study AA05228, n=25) among 50, 100, and 150mcg strengths following 600mcg dose.<br>BE was assessed using the baseline adjusted pharmacokinetic parameters and ratios (soft gel capsule vs. Synthroid) of LSM (90% confidence interval) were 1.030 (92.8-114.4) and 1.068 (100.7-113.2) for AUC and Cmax, respectively (n=28). Dosage form equivalence was concluded by the sponsor among 50, 100, and 150mcg strengths.<br><br>Means of the time to reach Cmax (Tmax) were 2.896 hour and 2.086 hour for the soft gel capsule and Synthroid®, respectively. |

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