CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-402

Clinical Pharmacology and Biopharmaceutics Review

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA #:	21-402	**RELEVANT IND #:**	———
BRAND NAME:	SYNTHROID	**GENERIC NAME:**	Levothyroxine sodium
STRENGTH(S):	25 – 300 mcg	**DOSAGE FORM:**	Tablet
APPLICANT:	Abbott Laboratories 200 Abbott Park Road, D-491, AP30-1E, Abbott Park, IL 60064-6157		
OCPB DIVISION:	DPE-2	**ORM DIVISION:**	DMEDP
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

MEMO

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the data submitted in a facsimile sent to the Agency on July 12, 2002, regarding the interim dissolution specification for SYNTHROID tablets. The interim specification of —— (Q) @ 45 minutes is acceptable to the Agency.

Steven B. Johnson, Pharm.D.
CPB Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader

APPEARS THIS WAY
ON ORIGINAL

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/s/

Steve Johnson
7/19/02 03:56:06 PM
BIOPHARMACEUTICS

Hae-Young Ahn
7/22/02 02:42:04 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number:	21-402	**Brand Name:**	SYNTHROID
OCPB Division (I, II, III):	DPE-2	**Generic Name:**	Levothyroxine Sodium
Clinical Division:	DMEDP	**Drug Class:**	Synthetic thyroxine
CPB Reviewer:	Steven B. Johnson, Pharm.D.	**Indication(s):**	Thyroid replace./suppression
CPB Team Leader:	Hae-Young Ahn, Ph.D.	**Dosage Form:**	Tablets
Submission Date:	31-JUL-2001 & 21-NOV-2001	**Dosing Regimen:**	QD (once daily)
CPB Review Due Date:	19-APR-2002	**Route of Administration:**	PO (oral)
Division Due Date:	2-MAY-2002	**Sponsor:**	Abbott Laboratories
PDUFA Date:	1-JUN-2002	**Priority Classification:**	5S

Clinical Pharmacology and Biopharmaceutics Information

Information Type	"X" if included at filing	# of Studies Submitted	# of Studies Reviewed	Critical Comments (if any)
Table of Contents	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bio- & Analytical Methods	X			
I. Clinical Pharmacology				
Mass Balance:				
Isozyme Characterization:				
Blood/Plasma Ratio:				
Plasma Protein Binding:				
Pharmacokinetics (PK) –				
– Healthy Volunteers –				
Single-Dose:				
Multiple-Dose:				
– Patients –				
Single-Dose:				
Multiple-Dose:				
Dose Proportionality –				
Single-Dose:				
Multiple-Dose:				
Drug-Drug Interaction Studies –				
In-vivo Effects ON Primary Drug:				
In-vivo Effects OF Primary Drug:				
In-vitro Studies:				
Subpopulation Studies –				
Ethnicity:				
Sex:				
Pediatrics:				
Geriatrics:				
Renal Impairment:				
Hepatic Impairment:				
Pharmacodynamics (PD) –				
Phase 2:	X	3		
Phase 3:				
PK / PD –				
Phase 1:				
Phase 2:				
Phase 3:				
Population Analyses –				
Rich Data Set:				
Sparse Data Set:				
II. Biopharmaceutics				
Absolute Bioavailability:				
Relative Bioavailability –				
Solution as Reference	X	1		
Other Formulation as Reference:	X	5		
Bioequivalence Studies –				
– Traditional Design –				
Single-Dose:	X	1		
Multiple-Dose:				

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– Replicate Design –				
Single-Dose:				
Multiple-Dose:				
Food-Drug Interaction Studies:	X	1		
Dissolution:	X	1		
In-vitro/In-vivo Correlation:	X	1		
BCS Based Biowaiver Request:				
BCS Classification Information:				
III. Other CPB Studies				
Genotype / Phenotype Studies:				
Chronopharmacokinetics:				
Pediatric Development Plan:				
Literature References:				
TOTAL # OF STUDIES		13	3	

Primary Reviewer Signature:	Steven B. Johnson, Pharm.D.	Date:	
Secondary Reviewer Signature:	Hae-Young Ahn, Ph.D.	Date:	

– Line Listing of Studies Included in this Application –

Study #	Study Title
2037	Evaluation of the effects of replacement/suppressive doses of L-thyroxine on the cardiovascular system.
2028	A pilot study of the effects of short-term withdrawal of SYNTHROID® thyroid hormone replacement in athyreotic patients. (01/97)
2001	A randomized, open-label, complete block, four-way crossover study to determine the comparative bioavailability of SYNTHROID® versus generic levothyroxine sodium tablets. (04/99)
2002	A PK study in normal human volunteers to compare the rate and extent of levothyroxine absorption from SYNTHROID® and LEVOXINE®. (02/97)
2061	A randomized, single-dose, parallel group study to evaluate the rate and extent of absorption of SYNTHROID® (levothyroxine sodium, USP) 75, 150, and 300 mcg tabs using an athyreotic patient model.
2020	A PK study in normal volunteers to compare the rate and extent of levothyroxine absorption from tablets manufactured by [redacted] (05/95)
2021	A PK study in normal volunteers to compare the rate and extent of absorption from SYNTHROID® and LEVOTHROID® tablets. (05/95)
2022	A PK study in normal volunteers to compare the rate and extent of levothyroxine absorption of tablets manufactured by [redacted] (06/95)
2044	A pilot study in normal volunteers to assess the feasibility of a novel model for estimating the kinetics of exogenous levothyroxine following oral administration. (12/96)
2036	A double-blind study in normal volunteers to compare the effects of the differences in *in vitro* dissolution on the *in vivo* rate and extent of absorption of levothyroxine sodium tablets. (12/96)
2033	**A PK study in normal volunteers to compare the rate and extent of absorption of two formulations of levothyroxine tablets following a high fat meal. (01/95)**
2032	A pilot study of the effects of SYNTHROID® (levothyroxine sodium) 25 mcg and 50 mcg tablets on TSH levels. (03/94)
M01-324	**A comparison of the bioavailability of a levothyroxine sodium tablet formulation (SYNTHROID) with that of a reference liquid formulation.**
M01-323	**Proportionality study of three different dosage form strengths of marketed levothyroxine sodium tablets (SYNTHROID).**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

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STRENGTH(S):	25 – 300 mcg	**DOSAGE FORM:**	Tablet
APPLICANT:	Abbott Laboratories 200 Abbott Park Road, D-491, AP30-1E, Abbott Park, IL 60064-6157		
LETTER DATE:	31-JUL-2001 & 21-NOV-2001	**PDUFA DATE:**	01-JUN-2002
OCPB DIVISION:	DPE-2	**ORM DIVISION:**	DMEDP
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

I. Executive Summary

Abbott Laboratories has submitted NDA 21-402 for SYNTHROID Brand of levothyroxine sodium tablets. This application contained 12 pharmacokinetic studies and relevant dissolution information for review. The two studies, which are recommended in the related "Guidance for Industry," included a relative bioavailability study that compared 2 x 300 mcg tablets with a 600 mcg oral solution, and a dosage-form proportionality study that compared 50 mcg, 100 mcg, and 300 mcg tablets. The dissolution method that was used for SYNTHROID followed the method outlined in the USP 24 Supplement 1 monograph for levothyroxine sodium tablets.

Of the remaining pharmacokinetic studies submitted in this application, none were chosen for review. The primary reason that these studies were not reviewed was they were relative bioequivalence studies that compared SYNTHROID with some other levothyroxine product, or the study designs were flawed such that a conclusion could not be reached.

The relative bioavailability study, M01-324, examined the relative rate and extent of exposure of a single dose of two 300 mcg levothyroxine tablets to a single dose of a 600 mcg oral solution in 29 normal healthy male and female subjects under fasting conditions. Results of this study showed that the relative bioavailability of two SYNTHROID 300 mcg tablets was approximately 93%. Both AUC_{0-48} and C_{max} were comparable between the formulations. T_{max} was expectedly prolonged when subjects were administered the tablet formulation (2.9 vs. 1.8 hours).

The dosage-form proportionality study, M01-323, compared a single dose of twelve 50 mcg, six 100 mcg and two 300 mcg tablets, each in 35 healthy normal male and female subjects under fasting conditions. Results clearly showed that proportionality was established between the 50 mcg and 100 mcg and 300 mcg tablets, for both AUC_{0-48} and C_{max}. The time to reach maximum concentration (T_{max}) was also similar between the strengths studied.

The dissolution method utilized in this application followed the one outlined in the USP 24 S1 monograph for levothyroxine sodium tablets. Multipoint dissolution data from three lots of each of the to-be-marketed strengths was included for evaluation. Results indicated that the method was appropriate for SYNTHROID, but that a new tolerance specification of ——— minutes should be used for this product.

Since the individual strength formulations were shown to be proportional, dosage-form equivalence was demonstrated between strengths representing the middle and extremes of the strength range, and dissolution was rapid, then biowaivers for the intermediate strengths not studied *in vivo* can be granted.

The DSI audit is scheduled to begin in May 2002 – results of the audit will be available prior to the PDUFA action date. – *Telephone conversation with Jacqueline O'Shaughnessy from DSI on 4/25/02.*

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed NDA 21-402 for SYNTHROID brand levothyroxine sodium tablets submitted by Abbott Laboratories and finds the application acceptable pending the final report from the Division of Scientific Investigations (DSI). Please convey the information described in the **Labeling** and **Comments to Firm** to the sponsor as appropriate.

Comments to Firm

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed Section 6 of NDA 21-402 for SYNTHROID brand of levothyroxine sodium tablets and has set the dissolution method and tolerance specifications as follows:

Apparatus Type	2 (paddles)
Media	[redacted]
Volume	500 mL
Speed of Rotation	50 RPM
Tolerance Specifications	**NLT [redacted] (Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes**

II. Table of Contents

III. Summary of CPB Findings

- Each of the [redacted] tablet strengths of SYNTHROID was found to be proportionally similar in formulation;
- The dissolution method [and specifications] were determined to be appropriate for SYNTHROID;
- The bioavailability of SYNTHROID, relative to an equivalent oral solution, was 93%;
- Dosage form equivalence was established between the 50, 100, and 300 mcg strengths; and
- Sufficient data was provided to support a biowaiver for the intermediate strengths that were not studied *in vivo*.

IV. QBR

Chemistry

Is the formulation for SYNTHROID proportional, by CFR definition, between strengths?

The formulation for SYNTHROID does exhibit proportionality between strengths, as defined in the CFR. The only differences between the strengths are the amount of active ingredient, levothyroxine sodium, and the colorants (see ***TABLE 1***).

TABLE 1: SYNTHROID formulation by strength

Ingredient	Amount (mg) per Tablet											
	25 mcg	50 mcg	75 mcg	88 mcg	100 mcg	112 mcg	125 mcg	137 mcg	150 mcg	175 mcg	200 mcg	300 mcg
Levothyroxine Sodium, USP	0.025	0.050	0.075	0.088	0.100	0.112	0.125	0.137	0.150	0.175	0.200	0.300
Lactose, Monohydrate, NF												
Confectioners Sugar, NF												
Acacia, NF												
Povidone, USP												
Magnesium Stearate, NF												
Talc, USP												
FD&C Yellow #6 Aluminum Lake	-	-	-	-	-	-	-	-	-	-	-	-
FD&C Red #40 Aluminum Lake	-	-	-	-	-	-	-	-	-	-	-	-
FD&C Blue #2 Aluminum Lake	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-
FD&C Blue #1 Aluminum Lake	-	-	-	-	-	-	-					
D&C Yellow #10 Aluminum Lake	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-
Total Tablet Weight	131.3	131.3	131.4	131.5	131.6	131.4	131.4	131.7	131.4	131.5	131.5	131.6

[1] FD&C Yellow #6, FD&C Red #40, FD&C Blue #1
[2] D&C Red #27, D&C Red #30
[3] FD&C Blue #1, FD&C Yellow #6, D&C Yellow #10

Dissolution

Is the dissolution method and tolerance specification appropriate for SYNTHROID tablets?

To answer this question, multipoint dissolution data from three lots of each of the to-be-marketed strengths was submitted to the original application using the dissolution method described in the USP 24 S1 monograph for levothyroxine sodium tablets (see ***TABLE 2***).

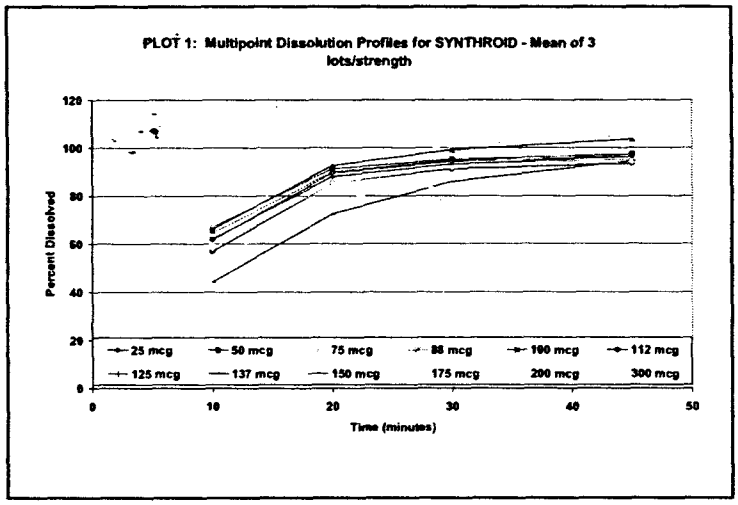
TABLE 2: USP 24 Supplement 1 Dissolution Method for Levothyroxine Sodium Tablets	
Apparatus Type	USP # 2 (paddles)
Media	
Volume	500 mL
Speed of Rotation	50 RPM
Sampling Times	10, 20, 30, and 45 minutes
Tolerance Specifications	(Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes

Results from this dissolution study showed that SYNTHROID tablets dissolve rapidly in the USP 24 S1 media. Inter- and intra-lot variability was generally low and inter-strength results were relatively consistent – except for the 137 mcg and 300 mcg strengths. In these cases, the early time points were considerably lower than the other strengths, but "caught up" by the last sampling point at 45 minutes (see ***TABLE 3*** and ***PLOT 1***). Based on the results of this data, the tolerance specifications for SYNTHROID should be set at (Q) @ 45 minutes.

TABLE 3: Multipoint dissolution profiles (lots used in the bioavailability studies are shaded)

	25 mcg			50 mcg			75 mcg			88 mcg			100 mcg			112 mcg		
Lot #	198830	198842	213293	222641	198606	198607	198907	198918	198903	210024	210026	198921	225713	281353	281355	198845	198844	198846
10																		
20																		
30																		
45																		

	125 mcg			137 mcg			150 mcg			175 mcg			200 mcg			300 mcg		
Lot #	198866	198889	198940	JYX-01-024	JYX-01-025	JYX-01-026	198800	198801	198805	210016	221088	227608	289617	281348	289662	105733	123489	154424
10																		
20																		
30																		
45																		



General Biopharmaceutics

What is the bioavailability of SYNTHROID tablets relative to an equivalent dose of an oral solution?

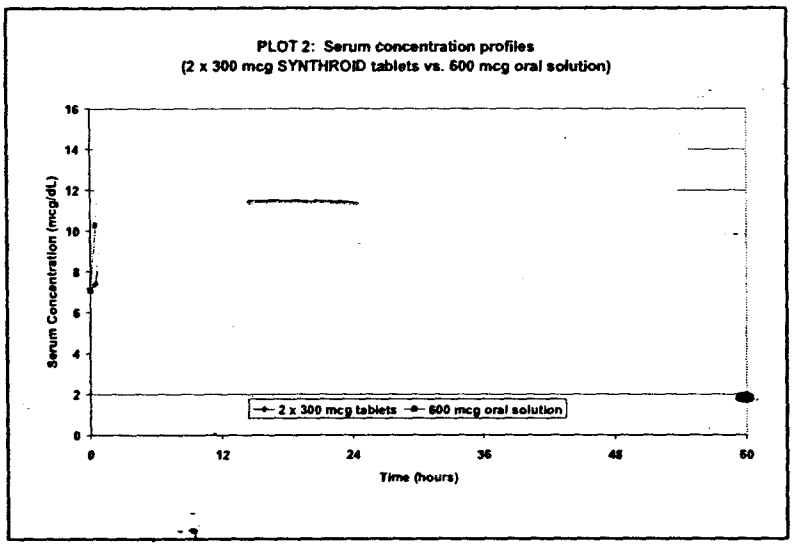
To determine the relative bioavailability of SYNTHROID tablets with an equivalent dose of an oral solution, a single-dose, open-label, randomized two-way crossover study was conducted in 32 (29 used for PK analysis) healthy male and female volunteers. Treatments consisted of administering (Tx A) 2 x 300 mcg SYNTHROID tablets (lot #: 0000105733) or (Tx B) a 600 mcg oral solution under fasting conditions. Treatments were separated by a 40 day washout period.

Results of study M01-324 show that the relative bioavailability of SYNTHROID tablets with an equivalent oral solution is approximately 93% (see ***TABLE 4*** and ***PLOT 2***).

TABLE 4: Relative bioavailability of SYNTHROID tablets versus an equivalent oral solution (600 mcg) - T_4

Parameter	Unit	TX A (2 x 300 mcg tabs)	Tx B (600 mcg sln)	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-48}	mcg*hr/dL	489.3 ± 65.2	529.5 ± 86.2	92.65	90.20	95.17
C_{max}	mcg/dL	13.2 ± 1.9	15.8 ± 2.9	84.24	81.25	87.33
T_{max}	h	2.9 ± 1.5	1.8 ± 0.8	—	—	—

Mean ± SD



Were representative strength brackets found to be dosage-form equivalent?
Study M01-323 examined the strength proportionality between different strengths of SYNTHROID tablets in a single-dose, open-label, three-period, six-sequence, randomized crossover study. Thirty-five male and female subjects were administered the following treatments: Tx A – 12 x 50 mcg tablets (lot #: 0000222641); Tx B – 6 x 100 mcg tablets (lot #: 0000225713); or Tx C – 2 x 300 mcg tablets (lot #: 0000105733). Each of the treatments was administered under fasting conditions and treatments were separated by 35-day washout periods.

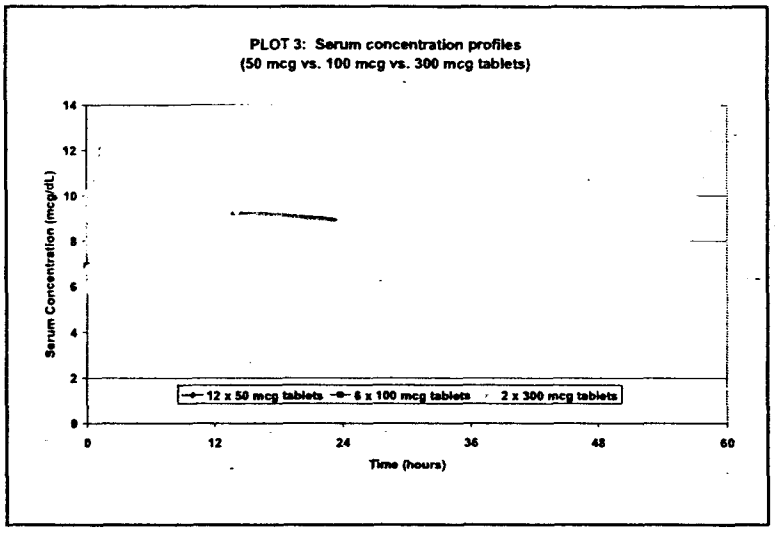
Data analysis was conducted using analysis of variance (ANOVA) with model terms sequence, subject nested within sequence, period, and treatment. Results of this study demonstrated that SYNTHROID 50 mcg, 100 mcg, and 300 mcg strength tablets are dosage-form equivalent for both AUC_{0-48} and C_{max}. In addition, T_{max} was similar between treatments A and C, but differed by more than 1-hour from treatment B. This difference in T_{max} was attributed to a single subject who had an apparent T_{max} at 36 hours post-dosing after treatment B. Evaluation of this subject's (ID 212) profile suggests that the 36-hour data point is an anomaly. (See **TABLES 5 & 6** and **PLOT 3**).

TABLE 5: Dosage-form equivalence of SYNTHROID tablets at equivalent doses (600 mcg)

Parameter	Unit	TX A (12 x 50 mcg tabs)	Tx B (6 x 100 mcg tabs)	Tx C (2 x 300 mcg tabs)
AUC_{0-48}	mcg*hr/dL	493.7 ± 76.8	488.5 ± 78.2	474.2 ± 70.7
C_{max}	mg/dL	13.4 ± 1.9	13.3 ± 2.15	12.9 ± 1.80
T_{max}	h	3.0 ± 2.2	4.1 ± 6.0	3.0 ± 2.3
Mean ± SD				

TABLE 6: Dosage-form equivalence of SYNTHROID tablets at equivalent doses (600 mcg)

Parameter	AUC_{0-48}			C_{max}		
	PE (%)	90% Confidence Intervals		PE (%)	90% Confidence Intervals	
		Low	High		Low	High
Tx A vs. Tx B	101.0	98.2	103.2	101.3	98.2	104.5
Tx C vs. Tx B	97.3	95.2	99.4	97.6	94.7	100.6
Tx C vs. Tx A	96.3	94.3	98.4	96.3	93.4	99.3



Biowaiver

Can the biowaiver request be granted for the nine tablet strengths that have not been clinically tested?

1. Three strengths of tablets, 50 mcg, 100 mcg, and 300 mcg, representing low, middle, and high strengths of the formulation, were found to be dosage-form equivalent.
2. Each strength tablet is proportionally similar in its active and inactive ingredients.
3. The final condition used to evaluate whether a biowaiver can be granted is based on multipoint dissolution testing. F_2 calculations are used to determine the degree of similarity between the dissolution curves and are based on the following criteria: 300 mcg serves as the reference for the 200, 175, 150, 137, 125, and 112 mcg strengths; 100 mcg serves as the references for the 88 and 75 mcg strengths; and 50 serves as the reference for the 25 mcg strength tablets. However, since the majority of dissolution sampling time points for SYNTHROID had dissolution values above—, it is assumed that the individual strengths are similar and will provide a respective strength bioavailability.

   The exception to the previous statement is the 137 mcg strength. F_2 criteria were applied to lot JYX-01-024 and it clearly failed: using 300 mcg, 100 mcg, and 50 mcg, respectively, as references. This lot also fails to meet the dissolution tolerance specification of —(Q) @ — minutes. However, since the two other 137 mg lots meet similarity criteria, sufficient data exists to qualify the strength for acceptance.

A biowaiver can be granted for the 9 intermediate strengths not studied in the *in vivo* studies.

Analytical

Have the analytical methods been sufficiently validated?

Human serum samples were analyzed for total thyroxine (T_4) to determine the bioavailability of levothyroxine sodium using a developed by . Analytical methods were found to be acceptable by the Agency. Results of the quality control analysis are presented in the following table:

	M01-324	M01-323
LLOQ (mcg/dL)		
Calibration (mcg/dL)		
Precision (%CV)		
Accuracy (%)		

V. Labeling

Because of the number of NDAs submitted for levothyroxine sodium products, DMEDP is using similar labeling for all levothyroxine sodium submissions. In the following section for pharmacokinetics, content must remain intact with the exception of agent specific information. (underlined).

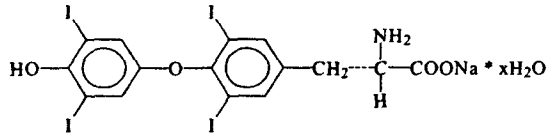
PHARMACOKINETICS

Absorption – Absorption of orally administered T_4 from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of SYNTHROID® tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%. T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption (see **PRECAUTIONS, Drug Interactions** and **Drug-Food Interactions**).

VI. Appendix

Proposed labeling
LEVOTHYROXINE LABELING TEMPLATE PREPARED BY FDA:
TRADEMARK ™ (levothyroxine sodium tablets, USP)

DESCRIPTION
---TRADEMARK™ (levothyroxine sodium tablets, USP) contain synthetic crystalline L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T_4 is identical to that produced in the human thyroid gland. Levothyroxine (T_4) sodium has an empirical formula of $C_{15}H_{10}I_4N\ NaO_4 \times H_2O$,



molecular weight of 798.86 g/mol (anhydrous), and structural formula as shown:
Inactive Ingredients

[Product-specific information supplied by applicant]

Strength (mcg)	Color additive(s)
	[Product-specific information supplied by applicant]

CLINICAL PHARMACOLOGY
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-stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), by the thyroid gland. Circulating serum T_3 and T_4 levels exert a feedback effect on both TRH and TSH secretion. When serum T_3 and T_4 levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increase.

The mechanisms by which thyroid hormones exert their physiologic actions are not completely understood, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T_3 and T_4 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.

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.

The physiologic actions of thyroid hormones are produced predominately by T_3, the majority of which (approximately 80%) is derived from T_4 by deiodination in peripheral tissues.

Levothyroxine, at doses individualized according to patient response, is effective as replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.

Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, Hashimoto's thyroiditis, multinodular goiter and, as adjunctive therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (see **INDICATIONS AND USAGE, PRECAUTIONS, DOSAGE ANDADMINISTRATION**).

PHARMACOKINETICS

Absorption – Absorption of orally administered T_4 from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of TRADEMARK tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately [***Product-specific information supplied by applicant***] %. T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption (see **PRECAUTIONS, Drug Interactions** and **Drug-Food Interactions**).

Distribution – Circulating thyroid hormones are greater than 99% bound to plasma proteins, including 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 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 (see **PRECAUTIONS, Drug Interactions** and **Drug-Laboratory Test Interactions**). Thyroid hormones do not readily cross the placental barrier (see **PRECAUTIONS, Pregnancy**).

Metabolism – T_4 is slowly eliminated (see **TABLE 1**). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent 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 (rT_3). T_3 and rT_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.

Table 1: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients				
Hormone	Ratio in Thyroglobulin	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%)[2]
Levothyroxine (T_4)	10 - 20	1	6-7[1]	99.96
Liothyronine (T_3)	1	4	≤ 2	99.5
[1] 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism; [2] Includes TBG, TBPA, and TBA				

INDICATIONS AND USAGE

Levothyroxine sodium is used for the following indications:

Hypothyroidism – As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total congenital absence of the thyroid gland, or from the effects of surgery, radiation, or drugs, with or without the presence of goiter.

Pituitary TSH Suppression – In the treatment or prevention of various types of euthyroid goiters (see **WARNINGS** and **PRECAUTIONS**), including thyroid nodules (see **WARNINGS** and **PRECAUTIONS**), subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter (see **WARNINGS** and **PRECAUTIONS**) and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

CONTRAINDICATIONS

Levothyroxine is contraindicated in patients with untreated subclinical (suppressed serum TSH level with normal T_3 and T_4 levels) or overt thyrotoxicosis of any etiology and in patients with acute myocardial infarction. Levothyroxine is contraindicated in patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see **PRECAUTIONS**). TRADEMARK is contraindicated in patients with hypersensitivity to any of the inactive ingredients in TRADEMARK tablets. (See **DESCRIPTION, Inactive Ingredients.**)

WARNINGS

WARNING: Thyroid hormones, including TRADEMARK, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

Levothyroxine sodium should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

In patients with nontoxic diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine sodium therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitationg overt thyrotoxicosis (see **Contraindications**). If the serum TSH level is not suprressed, Trademark should be used with caution in conjunction with careful monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential associated adverse cardiovascular signs and symptoms of hyperthyroidism.

PRECAUTIONS

General

Levothyroxine has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under-treatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Many drugs interact with levothyroxine sodium necessitating adjustments in dosing to maintain therapeutic response (see **Drug Interactions**).

Effects on bone mineral density- In women, long-term levothyroxine sodium therapy has been associated with decreased bone mineral density, especially in postmenopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Patients with underlying cardiovascular disease- Exercise caution when administering levothyroxine to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see **WARNINGS**; **PRECAUTIONS, Geriatric Use; and DOSAGE AND ADMINISTRATION**). If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Patients with nontoxic diffuse goiter or nodular thyroid disease - Exercise caution when administering levothyroxine to patients with nontoxic diffuse goiter or nodular thyroid disease in order to prevent precipitation of thyrotoxicosis (see **WARNINGS.**). If the serum TSH is already suppressed, levothyroxine sodium should not be administered (see **Contraindications**).

Associated endocrine disorders

Hypothalamic/pituitary hormone deficiencies- In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated (see **PRECAUTIONS, Autoimmune polyglandular syndrome** for adrenal insufficiency).

Autoimmune polyglandular syndrome- Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with levothyroxine sodium. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with levothyroxine (see **PRECAUTIONS, Drug Interactions**).

Other associated medical conditions

Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, with cardiovascular anomalies (pulmonary stenosis, atrial septal defect, and ventricular septal defect,) being the most common association.

Information for Patients

Patients should be informed of the following information to aid in the safe and effective use of TRADEMARK:

1. Notify your physician if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding or are taking any other medications, including prescription and over-the-counter preparations.
2. Notify your physician of any other medical conditions you may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems. Your dose of medications used to control these other conditions may need to be adjusted while you are taking TRADEMARK. If you have diabetes, monitor your blood and/or urinary glucose levels as directed by your physician and immediately report any changes to your physician. If you are taking anticoagulants (blood thinners), your clotting status should be checked frequently.
3. Use TRADEMARK only as prescribed by your physician. Do not discontinue or change the amount you take or how often you take it, unless directed to do so by your physician.
4. The levothyroxine in TRADEMARK is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis).

5. Take TRADEMARK as a single dose, preferably on an empty stomach, one-half to one hour before breakfast. Levothyroxine absorption is increased on an empty stomach.
6. It may take several weeks before you notice an improvement in your symptoms.
7. Notify your physician if you experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, heat intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.
8. Notify your physician if you become pregnant while taking TRADEMARK. It is likely that your dose of TRADEMARK will need to be increased while you are pregnant.
9. Notify your physician or dentist that you are taking TRADEMARK prior to any surgery.
10. Partial hair loss may occur rarely during the first few months of TRADEMARK therapy, but this is usually temporary.
11. TRADEMARK should not be used as a primary or adjunctive therapy in a weight control program.
12. Keep TRADEMARK out of the reach of children. Store TRADEMARK away from heat, moisture, and light.

Laboratory Tests

General

The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay (second generation assay sensitivity $\leq$ 0.1 mIU/L or third generation assay sensitivity $\leq$ 0.01 mIU/L) and measurement of free-T_4.

The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. The choice of laboratory tests depends on various factors including the etiology of the underlying thyroid disease, the presence of concomitant medical conditions, including pregnancy, and the use of concomitant medications (see **PRECAUTIONS, Drug Interactions and Drug-Laboratory Test Interactions**). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of TRADEMARK may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T_4 potency of the drug product.

Adults

In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels (using a sensitive assay) alone may be used to monitor therapy. The frequency of TSH monitoring during levothyroxine dose titration depends on the clinical situation but it is generally recommended at 6-8 week intervals until normalization. For patients who have recently initiated levothyroxine therapy and whose serum TSH has normalized or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured after 8-12 weeks. When the optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6-12 months, depending on the clinical situation, and whenever there is a change in the patient's status. It is recommended that a physical examination and a serum TSH measurement be performed at least annually in patients receiving TRADEMARK (see **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION**).

Pediatrics

In patients with congenital hypothyroidism, the adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free-T_4. During the first three years of life, the serum total- or free-T_4 should be maintained at all times in the upper half of the normal range. While the aim of therapy is to also normalize the serum TSH level, this is not always possible in a small percentage of patients, particularly in the first few months of therapy. TSH may not normalize due to a resetting of the pituitary-thyroid feedback threshold as a result of *in utero* hypothyroidism. Failure of the serum T_4 to increase into the upper half of the normal range within 2 weeks of initiation of TRADEMARK therapy and/or of the serum TSH to decrease below 20 mU/L within 4 weeks should alert the physician to the possibility that the child is not receiving adequate therapy. Careful inquiry should then be made regarding compliance, dose of medication administered, and method of administration prior to raising the dose of TRADEMARK.

The recommended frequency of monitoring of TSH and total or free T_4 in children is as follows: at 2 and 4 weeks after the initiation of treatment; every 1-2 months during the first year of life; every 2-3 months between 1 and 3 years of age; and every 3 to 12 months thereafter until growth is completed. More frequent intervals of monitoring may be necessary if poor compliance is suspected or abnormal values are obtained. It is

recommended that TSH and T_4 levels, and a physical examination, if indicated, be performed 2 weeks after any change in TRADEMARK dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals (see **PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION**).

Secondary (pituitary) and tertiary (hypothalamic) hypothyroidism

Adequacy of therapy should be assessed by measuring serum free-T_4 levels, which should be maintained in the upper half of the normal range in these patients.

Drug Interactions

Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to TRADEMARK. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and action of other drugs. A listing of drug-thyroidal axis interactions is contained in Table 2.

The list of drug-thyroidal axis interactions in Table 2 may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources. (e.g., package inserts of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

Table 2: Drug-Thyroidal Axis Interactions

Drug or Drug Class	Effect
Drugs that may reduce TSH secretion –the reduction is not sustained; therefore, hypothyroidism does not occur	
Dopamine / Dopamine Agonists Glucocorticoids Octreotide	Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: Dopamine (≥ 1 µg/kg/min); Glucocorticoids (hydrocortisone ≥ 100 mg/day or equivalent); Octreotide (> 100 µg/day).
Drugs that alter thyroid hormone secretion	
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodide (including iodine-containing Radiographic contrast agents) Lithium Methimazole Propylthiouracil (PTU) Sulfonamides Tolbutamide	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing Radiographic contrast agents)	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Drugs that may decrease T_4 absorption, which may result in hypothyroidism	
Antacids - Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Cation Exchange Resins - Kayexalate Ferrous Sulfate Sucralfate	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least 4 hours apart from these agents.
Drugs that may alter T_4 and T_3 serum transport - but FT_4 concentration remains normal; and, therefore, the patient remains euthyroid	
Drugs that may increase serum TBG concentration	**Drugs that may decrease serum TBG concentration**

Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
Drugs that may cause protein-binding site displacement	
Furosemide (> 80 mg IV) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs - Fenamates - Phenylbutazone Salicylates (> 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in FT_4. Continued administration results in a decrease in serum T_4 and normal FT_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total-T_4 levels may decrease by as much as 30%.
Drugs that may alter T_4 and T_3 metabolism	
Drugs that may increase hepatic metabolism, which may result in hypothyroidism	
Carbamazepine Hydantoins Phenobarbital Rifampin	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total- and free-T_4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.
Drugs that may decrease T_4 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists - (e.g., Propranolol > 160 mg/day) Glucocorticoids - (e.g., Dexamethasone $\geq$ 4 mg/day) Propylthiouracil (PTU)	Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (> 160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (see above).
Miscellaneous	
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.
Antidepressants - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline)	Concurrent use of tri/tetracyclic antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidediones - Insulin	Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.
Cardiac Glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.
Cytokines - Interferon-α - Interleukin-2	Therapy with interferon-α has been associated with the development of antithyroid microsomal antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients. Interferon-β and -γ have not been reported to cause thyroid dysfunction.
Growth Hormones - Somatrem - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators - (e.g., Theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic Agents	Thyroid hormones may reduce the uptake of ^{123}I, ^{131}I, and ^{99m}Tc.

Sympathomimetics	Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and / or TSH level alterations by various mechanisms.

Oral anticoagulants- Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the TRADEMARK dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see **Table 2**).

Digitalis glycosides- The therapeutic effects of digitalis glycosides may be reduced by levothyroxine. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see **Table 2**).

Drug-Food Interactions – Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the GI tract.

Drug-Laboratory Test Interactions – Changes in TBG concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free T_4 index (FT_4I). Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy (see also **Table 2**). Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

Carcinogenesis, Mutagenesis, and Impairment of Fertility – Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of levothyroxine. The synthetic T_4 in TRADEMARK is identical to that produced naturally by the human thyroid gland. Although there has been a reported association between prolonged thyroid hormone therapy and breast cancer, this has not been confirmed. Patients receiving TRADEMARK for appropriate clinical indications should be titrated to the lowest effective replacement dose.

Pregnancy – Category A – Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Therefore, the possibility of fetal harm appears remote. TRADEMARK should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. During pregnancy, serum T4 levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women taking TRADEMARK should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of TRADEMARK. Since postpartum TSH levels are similar to preconception values, the TRADEMARK dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-8 weeks postpartum.

Thyroid hormones do not readily cross the placental barrier; however, some transfer does occur as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent *in utero* hypothyroidism.

Nursing Mothers – Although thyroid hormones are excreted only minimally in human milk, caution should be exercised when TRADEMARK is administered to a nursing woman. However, adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

Pediatric Use

General

The goal of treatment in pediatric patients with hypothyroidism is to achieve and maintain normal intellectual and physical growth and development.

The initial dose of levothyroxine varies with age and body weight (see **DOSAGE AND ADMINISTRATION, Table 3**). Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters (see **PRECAUTIONS, Laboratory Tests**).

In children in whom a diagnosis of permanent hypothyroidism has not been established, it is recommended that levothyroxine administration be discontinued for a 30-day trial period, but only after the child is at least 3 years of age. Serum T_4 and TSH levels should then be obtained. If the T_4 is low and the TSH high, the diagnosis of permanent hypothyroidism is established, and levothyroxine therapy should be reinstituted. If the T_4 and TSH levels are normal, euthyroidism may be assumed and, therefore, the hypothyroidism can be considered to have been transient. In this instance, however, the physician should carefully monitor the child and repeat the thyroid function tests if any signs or symptoms of hypothyroidism develop. In this setting, the clinician should have a high index of suspicion of relapse. If the results of the levothyroxine withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, an alternate approach is to reduce the replacement dose of levothyroxine by half during the 30-day trial period. If, after 30 days, the serum TSH is elevated above 20 mU/L, the diagnosis of permanent hypothyroidism is confirmed, and full replacement therapy should be resumed. However, if the serum TSH has not risen to greater than 20mU/L, levothyroxine treatment should be discontinued for another 30-day trial period followed by repeat serum T_4 and TSH.

The presence of concomitant medical conditions should be considered in certain clinical circumstances and, if present, appropriately treated (see **PRECAUTIONS**).

Congenital Hypothyroidism (see **PRECAUTIONS, Laboratory Tests and DOSAGE and ADMINISTRATION**)

Rapid restoration of normal serum T_4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, TRADEMARK therapy should be initiated immediately upon diagnosis and is generally continued for life.

During the first 2 weeks of TRADEMARK therapy, infants should be closely monitored for cardiac overload, arrhythmias, and aspiration from avid suckling.

The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

Acquired Hypothyroidism in Pediatric Patients

The patient should be monitored closely to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

Geriatric Use

Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (see **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage. They include the following:

General: fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating;
Central nervous system: headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia;
Musculoskeletal: tremors, muscle weakness;
Cardiac: palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest;
Pulmonary: dyspnea;
GI: diarrhea, vomiting, abdominal cramps;
Dermatologic: hair loss, flushing;
Reproductive: menstrual irregularities, impaired fertility

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Seizures have been reported rarely with the institution of levothyroxine therapy.

Inadequate levothyroxine dosage will produce or fail to ameliorate the signs and symptoms of hypothyroidism.

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

OVERDOSAGE

The signs and symptoms of overdosage are those of hyperthyroidism (see **PRECAUTIONS** and **ADVERSE REACTIONS**). In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Seizures have occurred in a child ingesting approximately 20 mg of levothyroxine. Symptoms may not necessarily be evident or may not appear until several days after ingestion of levothyroxine sodium.

Treatment of Overdosage

Levothyroxine sodium should be reduced in dose or temporarily discontinued if signs or symptoms of overdosage occur.

> **Acute Massive Overdosage** – This may be a life-threatening emergency, therefore, symptomatic and supportive therapy should be instituted immediately. If not contraindicated (e.g., by seizures, coma, or loss of the gag reflex), the stomach should be emptied by emesis or gastric lavage to decrease gastrointestinal absorption. Activated charcoal or cholestyramine may also be used to decrease absorption. Central and peripheral increased sympathetic activity may be treated by administering B-receptor antagonists, e.g., propranolol (1 to 3 mg intravenously over a 10-minute period, or orally, 80 to 160 mg/day). Provide respiratory support as needed; control congestive heart failure; control fever, hypoglycemia, and fluid loss as necessary. Glucocorticoids may be given to inhibit the conversion of T_4 to T_3. Because T_4 is highly protein bound, very little drug will be removed by dialysis.

DOSAGE AND ADMINISTRATION

General Principles:

The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state. The goal of suppressive therapy is to inhibit growth and/or function of abnormal thyroid tissue. The dose of TRADEMARK that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see **WARNINGS** and **PRECAUTIONS**). Hence, the following recommendations serve only as dosing guidelines. Dosing must be individualized and adjustments made based

on periodic assessment of the patient's clinical response and laboratory parameters (see **PRECAUTIONS, Laboratory Tests**).

TRADEMARK is administered as a single daily dose, preferably one-half to one-hour before breakfast. TRADEMARK should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (see **PRECAUTIONS, Drug Interactions**).

Due to the long half-life of levothyroxine, the peak therapeutic effect at a given dose of levothyroxine may not be attained for 4-6 weeks.

Caution should be exercised when administering TRADEMARK to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (see **PRECAUTIONS**).

Specific Patient Populations:

Hypothyroidism in Adults and in Children in Whom Growth and Puberty are Complete (see **WARNINGS** and **PRECAUTIONS, Laboratory Tests**)

Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have been recently treated for hyperthyroidism or who have been hypothyroid for only a short time (such as a few months). The average full replacement dose of levothyroxine is approximately 1.7 mcg/kg/day (e.g., **100-125 mcg/day** for a 70 kg adult). Older patients may require less than 1 mcg/kg/day. Levothyroxine doses greater than 200 mcg/day are seldom required. An inadequate response to daily doses $\geq$ 300 mcg/day is rare and may indicate poor compliance, malabsorption, and/or drug interactions.

For most patients older than 50 years or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of **25-50 mcg/day** of levothyroxine is recommended, with gradual increments in dose at 6-8 week intervals, as needed. The recommended starting dose of levothyroxine in elderly patients with cardiac disease is **12.5-25 mcg/day**, with gradual dose increments at 4-6 week intervals. The levothyroxine dose is generally adjusted in 12.5-25 mcg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized.

In patients with severe hypothyroidism, the recommended initial levothyroxine dose is **12.5-25 mcg/day** with increases of 25 mcg/day every 2-4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized.

In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the levothyroxine dose should be titrated until the patient is clinically euthyroid and the serum free-T_4 level is restored to the upper half of the normal range.

Pediatric Dosage – Congenital or Acquired Hypothyroidism (see **PRECAUTIONS, Laboratory Tests**)

General Principles

In general, levothyroxine therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development.

Undertreatment and overtreatment should be avoided (see **PRECAUTIONS, Pediatric Use**).

TRADEMARK 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 1-2 teaspoons) of water. This suspension can be administered by spoon or dropper. **DO NOT STORE THE SUSPENSION.** Foods that decrease absorption of levothyroxine, such as soybean infant formula, should not be used for administering levothyroxine. (see **PRECAUTIONS , Drug-Food Interactions**).

Newborns

The recommended starting dose of levothyroxine in newborn infants is **10-15 mcg/kg/day**. A lower starting dose (e.g., 25 mcg/day) should be considered in infants at risk for cardiac failure, and the dose should be increased in 4-6 weeks as needed based on clinical and laboratory response to treatment. In infants with very low (< 5 mcg/dl) or undetectable serum T_4 concentrations, the recommended initial starting dose is **50 mcg/day** of levothyroxine.

Infants and Children

Levothyroxine therapy is usually initiated at full replacement doses, with the recommended dose per body weight decreasing with age (see **TABLE 3**). However, in children with chronic or severe hypothyroidism, an initial dose of **25 mcg/day** of levothyroxine is recommended with increments of 25 mcg every 2-4 weeks until the desired effect is achieved.

Hyperactivity in an older child can be minimized if the starting dose is one-fourth of the recommended full replacement dose, and the dose is then increased on a weekly basis by an amount equal to one-fourth the full-recommended replacement dose until the full recommended replacement dose is reached.

Table 3: Levothyroxine Dosing Guidelines for Pediatric Hypothyroidism	
AGE	**Daily Dose Per Kg Body Weight[a]**
0-3 months	**10-15 mcg/kg/day**
3-6 months	**8-10 mcg/kg/day**
6-12 months	**6-8 mcg/kg/day**
1-5 years	**5-6 mcg/kg/day**
6-12 years	**4-5 mcg/kg/day**
>12 years	**2-3 mcg/kg/day**
Growth and puberty complete	**1.7 mcg/kg/day**
[a] The dose should be adjusted based on clinical response and laboratory parameters (**see PRECAUTIONS, Laboratory Tests and Pediatric Use**).	

(i)

(ii)

Pregnancy- Pregnancy may increase levothyroxine requirements (see **PREGNANCY**).

Subclinical Hypothyroidism- If this condition is treated, a lower levothyroxine dose (e.g., **1 mcg/kg/day**) than that used for full replacement may be adequate to normalize the serum TSH level. Patients who are not treated should be monitored yearly for changes in clinical status and thyroid laboratory parameters.

TSH Suppression in Well-differentiated Thyroid Cancer and Thyroid Nodules –The target level for TSH suppression in these conditions has not been established with controlled studies. In addition, the efficacy of TSH suppression for benign nodular disease is controversial. Therefore, the dose of TRADEMARK used for TSH suppression should be individulaized based on the specific disease and the patient being treated.

In the treatment of well-differentiated (papillary and follicular) thyroid cancer, levothyroxine is used as an adjunct to surgery and radioiodine therapy. Generally, TSH is suppressed to <0.1 mU/L, and this usually requires a levothyroxine dose of **greater than 2 mcg/kg/day**. However, in patients with high-risk tumors, the target level for TSH suppression may be <0.01 mU/L.

In the treatment of benign nodules and nontoxic multinodular goiter, TSH is generally suppressed to a higher target (e.g. 0.1-0.5 mU/L for nodules and 0.5-1.0 mU/L for multinodular goiter) than that used for the treatment of thyroid cancer. Levothyroxine sodium is contraindicated if the serum TSH is already suppressed due to the risk of precipitating overt thyrotoxicosis (see **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS**).

Myxedema Coma – Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral thyroid hormone drug products are not recommended to treat this condition. Thyroid hormone drug products formulated for intravenous administration should be administered.

HOW SUPPLIED

—TRADEMARK™ (levothyroxine sodium tablets, USP) are *[Product-specific information supplied by applicant]*

Strength (mcg)	Color	NDC # for bottles of (count)	NDC # for bottles of (count)

STORAGE CONDITIONS
[Product-specific information supplied by applicant]

Rx ONLY

MANUFACTURER
[Product-specific information supplied by applicant]

Individual Study Reviews

2.0 Synopsis

Abbott Laboratories **Name of Study Drug:** SYNTHROID® **Name of Active Ingredient:** Levothyroxine Sodium	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only):**

Title of Study: A Comparison of the Bioavailability of a Levothyroxine Sodium Tablet Formulation (SYNTHROID®) with that of a Reference Liquid Formulation

Investigator: Robert O'Dea, PhD, MD

Study Site: Abbott Clinical Pharmacology Research Unit
Waukegan, IL 60085

Publication (Reference): Not applicable.

Studied Period: **Study Initiation Date:** 05 June 2001 **Date First Subject Dosed:** 21 June 2001 **Date Last Subject Completed Dosing:** 31 July 2001 **Study Completion Date:** 13 August 2001	**Phase of Development:** 1

Objective: The objective of this study was to determine the bioavailability of a tablet formulation of levothyroxine sodium (SYNTHROID®) relative to that of a reconstituted solution formulation of SYNTHROID® administered orally.

Methodology: This Phase 1, single-dose, open-label, randomized study was conducted according to a two-period, crossover design. The total dose given for each regimen in the study was 600 µg levothyroxine sodium. Subjects received one of two sequences of Regimen A (two 300 µg SYNTHROID® tablets) and Regimen B (15 mL SYNTHROID® reconstituted solution containing 600 µg levothyroxine sodium) under fasting conditions at approximately 0800 on Study Day 1 of each period. A washout interval of 40 days separated the doses of the two study periods.

Blood samples for total levothyroxine (T_4) and total triiodothyronine (T_3) were collected into [redacted] collection tubes at 0.5 hours prior, 0.25 hours prior, and immediately prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 hours after dosing in each study period. Sufficient blood was collected to provide 3 mL serum from each sample.

Serum concentrations of T_4 and T_3 were determined using [redacted] methods at [redacted] The lower limit of quantitation of T_4 was [redacted] using a 25 µL serum sample. The lower limit of quantitation of T_3 was [redacted] using a 100 µL serum sample. Samples were analyzed between the dates of 06 August 2001 and 17 August 2001.

Number of Subjects:

Planned: 32; Entered: 32; Completed: 29; Evaluated for Safety: 32; Evaluated for Pharmacokinetics: 29

For the 32 subjects who participated in the study, the mean age was 31.6 years (ranging from 18 to 50 years), the mean weight was 73.3 kg (ranging from 58 to 93 kg) and the mean height was 170.4 cm (ranging from 148 to 188 cm). For the 29 subjects (15 males and 14 females) included in the pharmacokinetic analyses, the mean age was 31.3 years (ranging from 18 to 50 years), the mean weight was 73.9 kg (ranging from 58 to 93 kg) and the mean height was 170.7cm (ranging from 148 to 188 cm).

Diagnosis and Main Criteria for Inclusion: Subjects were male and female volunteers between 18 and 50 years of age, inclusive. Subjects in the study were judged to be euthyroid and in general good health based on the results of a medical history, physical examination, laboratory profile and electrocardiogram (ECG). Females were postmenopausal, sterile or if of childbearing potential, were not pregnant or nursing and were practicing an acceptable method of birth control.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

	Regimen	
	A (Test)	**B (Reference)**
Dosage Form	SYNTHROID® Tablet	SYNTHROID®
Strength	300 µg	200 µg/vial
Mode of Administration	Oral	Oral
NDC	0048-1170-03	0048-1014-99
Bulk Product Lot Number	0000105733	0000089907
Potency (% of Label Claim)	Release: 02 July 2001: 31 July 2001:	Release: 18 January 2001:
Manufacturing Site+		
Manufacturing Date	07 August 2000	26 August 2000
Theoretical Batch Size		
Expiration Date	August 2002	August 2002

Duration of Treatment: Two single 600 µg doses of levothyroxine sodium were administered, one dose on each of 21 June 2001 and 31 July 2001.

Criteria for Evaluation:

Pharmacokinetic: The pharmacokinetic parameter values of levothyroxine (T_4) and triiodothyronine (T_3) were estimated using noncompartmental methods. These included the maximum concentration (C_{max}), the time to C_{max} (T_{max}) and the area under the serum concentration-time curve from time 0 to 48 hours (AUC_{48}). For each subject and each regimen, the last measurable concentration for both T_3 and T_4 was at 48 hours.

Safety: Safety was evaluated based on adverse event, physical examination, vital signs and laboratory tests assessments.

Statistical Methods:

Pharmacokinetic: Analyses of variance (ANOVAs) with fixed effects for sex, sequence, sex-by-sequence interaction, period, regimen and the interaction of sex with each of period and regimen, and with random

effects for subjects nested within sex-by-sequence combination were performed for T_{max} and the natural logarithms of C_{max} and AUC. A significance level of 0.05 was used for all tests.

The bioavailability of Regimen A (tablet) relative to that of Regimen B (solution) was assessed by the two one-sided tests procedure *via* 90% confidence intervals obtained from the analyses of the natural logarithms of AUC and C_{max}.

Safety: The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by COSTART V term and body system with a breakdown by regimen. Laboratory test values outside the reference ranges were identified.

Summary/Conclusions:

Pharmacokinetic Results: Mean ± standard deviation (SD) pharmacokinetic parameters for levothyroxine (T_4) and triiodothyronine (T_3) are listed in the following table.

Pharmacokinetic Parameters (units)		Regimen£ A	Regimen£ B	(units)	A	B
		T_4			T_3	
N		29	29		29	29
T_{max}	(h)	2.9 ± 1.5*	1.8 ± 0.8	(h)	19.2 ± 20.1	15.3 ± 16.8
C_{max}	(µg/dL)	13.2 ± 1.9*	15.8 ± 2.9	(ng/mL)	1.46 ± 0.21*	1.56 ± 0.21
AUC_{48}	(µg•h/dL)	489.3 ± 65.2*	529.5 ± 86.2	(ng•h/mL)	62.4 ± 8.4*	65.7 ± 8.6

£ Regimen A: 2 x 300 µg SYNTHROID® tablets administered under fasting conditions.
Regimen B: 15 mL SYNTHROID® solution containing 600 µg levothyroxine sodium administered under fasting conditions.

* Statistically significantly different from solution formulation (Regimen B, ANOVA, $p < 0.05$).

The bioequivalence/bioavailability results are listed in the following table.

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Values* Test	Central Values* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
		Levothyroxine (T_4)			
A *vs.* B	C_{max} (µg/dL)	13.153	15.601	0.843	0.813 – 0.874
	AUC_{48} (µg•h/dL)	486.694	524.805	0.927	0.903 – 0.953
		Triiodothyronine (T_3)			
A *vs.* B	C_{max} (ng/mL)	1.449	1.550	0.935	0.913 – 0.957
	AUC_{48} (ng•h/mL)	61.863	65.338	0.947	0.925 – 0.969

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

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R&D/01/471

Safety Results: The regimens tested were generally well tolerated by the subjects. No clinically significant physical examination results, vital signs or adverse event profiles were observed during the course of the study, except for the presence of rash in Subject 107. All clinically significant laboratory values reported throughout the study were considered not related to the study drug.

The proportion of subjects reporting at least one treatment-emergent adverse event was slightly higher among subjects who received Regimen A (33.3%) than those who received Regimen B (22.6%). The most common treatment-emergent adverse events (reported by two or more subjects in any regimen) were headache, vasodilatation and nausea. The majority of adverse events were assessed by the investigator as possibly or probably related to study drug and mild or moderate in severity.

There were no deaths or other serious adverse events. Two subjects discontinued from the study due to the occurrence of at least one adverse event. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for vital signs, ECGs and physical examinations were unremarkable for each treatment group.

Conclusions: The relative bioavailability of SYNTHROID® tablets compared to an equal nominal dose of oral levothyroxine sodium solution is estimated to be 93%. The SYNTHROID® tablet formulation (Regimen A) was bioequivalent to the SYNTHROID® reconstituted solution formulation (Regimen B) because the 90% confidence intervals for evaluating bioequivalence were contained within the ⟶ range for both T_4 and T_3. Equivalence was based on the results of the two one-sided tests procedure from the analyses of log-transformed AUC_{48} and C_{max}.

The regimens tested were generally well tolerated by the subjects. There were no apparent differences between the regimens with respect to safety.

Date of Report: 11 October 2001

2.0 Synopsis

Abbott Laboratories **Name of Study Drug:** SYNTHROID® **Name of Active Ingredient:** Levothyroxine Sodium	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only):**

Title of Study: Proportionality study of three different dosage-form strengths of marketed levothyroxine sodium tablets (SYNTHROID®)

Investigator: Robert F. O'Dea, PhD. MD

Study Site: Abbott Clinical Pharmacology Research Unit
Waukegan, IL

Publication (Reference): Not applicable.

Studied Period: **Study Initiation Date:** 04 June 2001 **Date First Subject Dosed:** 18 June 2001 **Date Last Subject Completed Dosing:** 27 August 2001 **Study Completion Date:** 04 September 2001	**Phase of Development:** 1

Objective: The objective of this study was to determine the dosage-form proportionality among low, middle and high marketed-tablet strengths of SYNTHROID® (levothyroxine sodium).

Methodology: This Phase 1, single-dose, open-label, randomized study was conducted according to a three-period, six-sequence, crossover design. The total dose given for each regimen in the study was 600 µg levothyroxine sodium. Subjects received one of six sequences of Regimen A (twelve 50 µg SYNTHROID® tablets), Regimen B (six 100 µg SYNTHROID® tablets) and Regimen C (two 300 µg SYNTHROID® tablets) under fasting conditions at approximately 0800 on Study Day 1 of each period. A washout interval of 35 days separated the doses in consecutive study periods.

Blood samples for total levothyroxine (T_4) and total triiodothyronine (T_3) were collected into [redacted] collection tubes at 0.5 hours prior, 0.25 hours prior, and immediately prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 hours after dosing in each study period. Sufficient blood was collected to provide 3 mL serum from each sample.

Serum concentrations of T_4 and T_3 were determined using [redacted] methods at [redacted]. The lower limit of quantitation of T_4 was [redacted] using a 25 µL serum sample. The lower limit of quantitation of T_3 was [redacted] using a 100 µL serum sample. Samples were analyzed between the dates of 05 September 2001 and 26 September 2001.

Number of Subjects:

Planned: 36; Entered: 36; Completed: 34; Evaluated for Safety: 36; Evaluated for Pharmacokinetics: 35

For the 36 subjects (18 males and 18 females) who participated in the study, the mean age was 33.6 years (ranging from 18 to 50 years), the mean weight was 75.6 kg (ranging from 57 to 98 kg) and the mean height was 173.8 cm (ranging from 156 to 192 cm). For the 35 subjects (18 males and 17 females) included in the pharmacokinetic analyses, the mean age was 33.9 years (ranging from 18 to 50 years), the mean weight was 75.4 kg (ranging from 57 to 98 kg) and the mean height was 173.9 cm (ranging from 156 to 192 cm).

Diagnosis and Main Criteria for Inclusion: Subjects were male and female volunteers between 18 and 50 years of age, inclusive. Subjects in the study were judged to be euthyroid and in general good health based on the results of a medical history, physical examination, laboratory profile and electrocardiogram (ECG). Females were postmenopausal, sterile or if of childbearing potential, were not pregnant or nursing and were practicing an acceptable method of birth control.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

	Regimen		
	A	B	C
Dosage Form	SYNTHROID® Tablet	SYNTHROID® Tablet	SYNTHROID® Tablet
Strength	50 µg	100 µg	300 µg
Mode of Administration	Oral	Oral	Oral
NDC	0048-1040-03	0048-1070-03	0048-1170-03
Bulk Product Lot Number	0000222641	0000225713	0000105733
Potency (% of Label Claim)	02 July 2001: — 31 July 2001: — 24 August 2001: —	22 June 2001: — 27 July 2001: — 24 August 2001: —	02 July 2001: — 31 July 2001: — 24 August 2001: —
Manufacturing Site+	—	—	—
Manufacturing Date	31 January 2001	29 January 2001	07 August 2000
Batch Size	—	—	—
Expiration Date	October 2002	January 2003	August 2002

Duration of Treatment: Three single 600 µg doses of levothyroxine sodium were administered, one dose on each of 18 June 2001, 23 July 2001 and 27 August 2001.

Criteria for Evaluation:

Pharmacokinetic: The pharmacokinetic parameter values of levothyroxine (T_4) and triiodothyronine (T_3) were estimated using noncompartmental methods. These included the maximum concentration (C_{max}), the time to C_{max} (T_{max}) and the area under the serum concentration-time curve from time 0 to 48 hours (AUC_{48}). For each subject and each regimen, the last measurable concentration for both T_3 and T_4 was at 48 hours.

Safety: Safety was evaluated based on adverse event, physical examination, vital signs and laboratory tests assessments.

Statistical Methods:

Pharmacokinetic: Analyses of variance (ANOVAs) with fixed effects for sex, sequence, sex-by-sequence interaction, period, regimen and the interaction of sex with each of period and regimen, and with random effects for subjects nested within sex-by-sequence combination were performed for T_{max} and the natural logarithms of C_{max} and AUC_{48}. A significance level of 0.05 was used for all tests.

The bioavailability of Regimens A and C (test) relative to that of the Regimen B (reference) was assessed by the two one-sided tests procedure *via* 90% confidence intervals obtained from the analyses of the natural logarithms of AUC_{48} and C_{max}. The bioavailability of Regimens A and C were also compared. Bioequivalence was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC_{48} and C_{max} were within the ——— range.

Safety: The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by COSTART V term and body system with a breakdown by regimen. Laboratory test values outside the reference ranges were identified.

Summary/Conclusions:

Pharmacokinetic Results: Mean ± standard deviation (SD) pharmacokinetic parameters of levothyroxine (T_4) and triiodothyronine (T_3) are listed in the following table.

Pharmacokinetic Parameters (units)		Regimen£ A (N = 34)	B (N = 35)	C (N = 35)
			T_4	
T_{max}	(h)	3.0 ± 2.2	4.1 ± 6.0	3.0 ± 2.3
C_{max}	(µg/dL)	13.4 ± 1.90	13.3 ± 2.15	12.9 ± 1.80#
AUC_{48}	(µg•h/dL)	493.7 ± 76.8	488.5 ± 78.2	474.2 ± 70.7*,#
			T_3	
T_{max}	(h)	14.0 ± 15.3	13.2 ± 16.5	16.6 ± 19.3
C_{max}	(ng/mL)	1.47 ± 0.16	1.46 ± 0.16	1.46 ± 0.18
AUC_{48}	(ng•h/mL)	61.7 ± 6.3	60.9 ± 7.4	61.4 ± 7.6

£ Regimen A: Twelve 50 µg SYNTHROID® tablets administered under fasting conditions.
Regimen B: Six 100 µg SYNTHROID® tablets administered under fasting conditions.
Regimen C: Two 300 µg SYNTHROID® tablets administered under fasting conditions.

* Statistically significantly different from 100 µg tablet regimen (Regimen B, ANOVA, $p < 0.05$).

\# Statistically significantly different from 50 µg tablet regimen (Regimen A, ANOVA, $p < 0.05$).

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Study M01-323
R&D/01/470

The bioequivalence/bioavailability results are listed in the following table.

Regimens I *vs.* II	Pharmacokinetic Parameter	Central Values* Regimen I	Central Values* Regimen II	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
			Levothyroxine (T_4)		
A *vs.* B	C_{max} (µg/dL)	13.311	13.140	1.013	0.982 – 1.045
	AUC_{48} (µg•h/dL)	487.657	482.939	1.010	0.988 – 1.032
C *vs.* B	C_{max} (µg/dL)	12.823	13.140	0.976	0.947 – 1.006
	AUC_{48} (µg•h/dL)	469.721	482.939	0.973	0.952 – 0.994
C *vs.* A	C_{max} (µg/dL)	12.823	13.311	0.963	0.934 – 0.993
	AUC_{48} (µg•h/dL)	469.721	487.657	0.963	0.943 – 0.984
			Triiodothyronine (T_3)		
A *vs.* B	C_{max} (ng/mL)	1.457	1.450	1.005	0.978 – 1.032
	AUC_{48} (ng•h/mL)	61.062	60.376	1.011	0.991 – 1.032
C *vs.* B	C_{max} (ng/mL)	1.449	1.450	1.000	0.973 – 1.027
	AUC_{48} (ng•h/mL)	60.934	60.376	1.009	0.989 – 1.030
C *vs.* A	C_{max} (ng/mL)	1.449	1.457	0.995	0.969 – 1.022
	AUC_{48} (ng•h/mL)	60.934	61.062	0.998	0.978 – 1.018

* Antilogarithms of the least squares means for logarithms.
\+ Antilogarithm of the difference (I minus II) of the least squares means for logarithms.

Safety Results: The regimens tested were generally well tolerated by the subjects. No clinically significant physical examination results, vital signs, clinical laboratory values or adverse event profiles were observed during the course of the study.

The proportion of subjects reporting at least one treatment-emergent adverse event was slightly higher for Regimens A and C (20.6% and 17.1%, respectively) than it was for Regimen B (13.9%). The most common treatment-emergent adverse event (reported by two or more subjects in any regimen) was headache. The majority of adverse events were assessed by the investigator as possibly or probably related to study drug and 44 of the treatment-emergent adverse events were rated as mild, two as moderate and one as severe. There were no deaths, serious adverse events or other significant adverse events reported during the study.

Conclusions: The 50 µg, 100 µg and 300 µg SYNTHROID® tablet strengths were dosage-form proportional as Regimen A (12 x 50 µg), Regimen B (6 x 100 µg) and Regimen C (2 x 300 µg) were bioequivalent to each other. Bioequivalence was concluded because the 90% confidence intervals for evaluating bioequivalence were contained within the ——— range for both T_4 and T_3, and for each pair of regimens. Equivalence was based on the results of the two one-sided tests procedure from the analyses of log-transformed AUC_{48} and C_{max}.

The regimens tested were generally well tolerated by the subjects. No clinically significant physical examination results, vital signs or laboratory measurements, or adverse event profiles were observed during the course of the study. There were no apparent differences among the regimens with respect to safety.

Date of Report: 02 November 2001

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/s/

Steve Johnson
7/22/02 10:49:58 AM
BIOPHARMACEUTICS

Review completed - acceptable pending DSI audit results

Hae-Young Ahn
7/22/02 02:44:52 PM
BIOPHARMACEUTICS

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/s/

Steve Johnson
9/17/01 12:34:11 PM
BIOPHARMACEUTICS
Amount of dissolution information is sufficient for review [i.e., 3 lo
ts x 12 strengths; USP 24 S1]

Hae-Young Ahn
9/17/01 02:15:03 PM
BIOPHARMACEUTICS