

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-292

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-292 N000/A2
Generic Name: Levothyroxine Sodium
Strength(s): 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets
Sponsor: Genpharm Incorporated
 85 Advance Road, Etobicoke, Ontario, Canada M8Z2S9
Submission Date: 03-DEC-01
Submission Type: New Drug Application
Reviewer: Steven B. Johnson, Pharm.D.

On 8-MAY-2001, the Agency issued an "approvable" (AE) letter to Genpharm for their levothyroxine sodium tablet product. In the Biopharmaceutics section of that AE letter, a dissolution method and tolerance specification was recommended (see TABLE 1). This method was chosen from among — different methods. In this present amendment, the sponsor acknowledges changing their method to the one described in the 8-MAY-2001 letter, with the following permutation:

The media volume for the 200 mcg and 300 mcg strengths will be conducted in _____ of media — the rest of the strengths will use _____ of media.

Since the solubility of levothyroxine sodium in a _____ is approximately _____ conditions cannot be maintained for the 200 and 300 mcg strengths using a media volume of _____. The Agency agrees with this conclusion. Please refer to TABLE 2, below, for the revised dissolution method.

TABLE 1: Genpharm Dissolution Method – Levothyroxine sodium	
Media:	
Volume:	
Apparatus:	USP apparatus 2 (paddles)
Speed:	
Tolerances:	

TABLE 2: Revised Genpharm Dissolution Method – Levothyroxine sodium		
	25 mcg – 175 mcg	200 mcg – 300 mcg
Media:		
Volume:		
Apparatus:	USP apparatus 2 (paddles)	USP apparatus 2 (paddles)
Speed:		
Tolerances:		

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RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed amendment A2 from NDA 21-137 and finds it acceptable. Please convey the following to the sponsor:

The dissolution specification for the GenPharm levothyroxine sodium tablets should be as follows:

	25 mca - 175 mcg	200 mcg - 300 mcg
Media:	_____	_____
Volume:	_____	_____
Apparatus:	USP apparatus 2 (paddles)	USP apparatus 2 (paddles)
Speed:	_____	_____
Tolerances:	_____	_____

Steven B. Johnson, Pharm.D.
CPB Reviewer

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

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/s/

Steve Johnson
4/10/02 12:02:51 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/10/02 04:22:06 PM
BIOPHARMACEUTICS

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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	21-292	Brand Name	
OCPB Division (I, II, III)	2	Generic Name	Levothyroxine
Medical Division	DMEDP	Drug Class	Synthetic T ₄
OCPB Reviewer	Steven B. Johnson	Indication(s)	Hypothyroidism
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Tablet
		Dosing Regimen	QD
Date of Submission	6-JUL-00	Route of Administration	PO
Estimated Due Date of OCPB Review	6-MAR-01	Sponsor	Genpharm
PDUFA Due Date	4-MAY-01	Priority Classification	Standard
Division Due Date	6-APR-01		

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				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				

Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
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	X			
Total Number of Studies		3	3	Primary issue = dissolution
Fiability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X			
QBR questions (key issues to be considered)				
Other comments or information not included above	See review			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-292, HFD-850(Lee), HFD-510(CSO), HFD-8XX(Ahh, Malinowski, HuntJ), CDR

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Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-292	Relevant IND:	59,041
Brand Name:	[TRADENAME]	Generic Name:	Levothyroxine Sodium
Strength(s):	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets		
Sponsor:	Genpharm Incorporated 85 Advance Road, Etobicoke, Ontario, Canada M8Z2S9		
Submission Date:	6-JUL-00; 9-AUG-00; 9-NOV-00; 10-APR-01		
Submission Type:	New Drug Application		
Reviewer:	Steven B. Johnson, B.S.Pharm, Pharm.D.		

Terms and Abbreviations

Agency _____	Food and Drug Administration
AUC _____	Area under the plasma-concentration-time curve
BA _____	Bioavailability
BE _____	Bioequivalence
C _{max} _____	Maximum drug concentration
DMEDP _____	Division of Metabolic and Endocrine Drug Products
DSI _____	Division of Scientific Investigation
Industry _____	Pharmaceutical Industry
OCPB _____	Office of Clinical Pharmacology and Biopharmaceutics
NDA _____	New Drug Application
NTR _____	Narrow therapeutic range
T _{max} _____	Time of maximum drug concentration
T ₄ _____	Levothyroxine
T ₃ _____	Triiodothyronine
rT ₃ _____	Reverse triiodothyronine
t _{1/2} _____	Drug elimination half-life

Synopsis

Genpharm Incorporated has submitted NDA 21-292 for levothyroxine sodium tablets. The original application contained three clinical pharmacokinetics studies and relevant dissolution information for review. Of the three studies submitted, one was a relative bioavailability study that compared 2 x 300 mcg tablets with a 600 mcg oral solution, and the other two were dosage-form proportionality studies that compared 50 mcg and 100 mcg tablets, and 100 mcg and 300 mcg tablets, respectively. The dissolution method that was initially used for Genpharm product followed the method outlined in the USP 23 monograph for levothyroxine sodium tablets. This method is unacceptable to the Agency for reasons which are discussed under the Dissolution section of this review. Therefore, additional multipoint dissolution data was asked for by the Agency to support a biowaiver for the intermediate strength tablets not evaluated in the dosage-form proportionality studies. This additional dissolution data was reviewed and was considered acceptable by the Agency.

The relative bioavailability study, 436-99-263, 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 24 healthy normal subjects under fasting conditions. Results of this study show that the relative bioavailability of two Genpharm 300 mcg tablets is approximately 98.8%. Both AUC₀₋₄₈ and C_{max} were comparable between formulations. However, T_{max} was expectedly prolonged when subjects were administered the tablet formulation (2.46 ± 0.95 vs. 1.69 ± 0.79; Mean ± SD).

The two dosage-form proportionality studies, 436-99-264 and 436-99-277, compared a single dose twelve 50 mcg tablets with a single dose of six 100 mcg tablets, and six 100 mcg tablets with two 300 mcg tablets,

respectively, each in 24 healthy normal subjects under fasting conditions. Results of these studies were positive in that proportionality was established between the 50 mcg and 100 mcg tablets, and the 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.

As mentioned previously, the original submission included multipoint dissolution data generated using the USP 23 monograph for levothyroxine sodium tablets. The company was informed that this method was unacceptable to the Agency and was asked to submit additional information. Presently, the USP 24 method must be followed in order for a sponsor to be granted a USP designation for their product. The sponsor has complied with these conditions by developing an in-house method for day-to-day quality control measures, and is using the USP 24 method so that they can get a USP designation. The in-house method utilizes _____

Results of this in-house method were found to be acceptable. They are also able to achieve the USP 24 dissolution method specifications.

The DSI audit concluded that the analytical data for total T4 were acceptable for Agency review (see *Appendix - DSI Audit*).

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-292 submitted 6-JUL-00. The overall Human Pharmacokinetics Section was found to be acceptable to the Agency. Please convey the *Comments to the Sponsor* as appropriate.

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Appendix Index

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436-99-263	Open-label, single-dose, two-period, randomized crossover, fasting bioavailability study of levothyroxine 600 µg, given in 300 µg (2 tablets) versus an oral solution at an equivalent dose in normal, healthy male and female volunteers.	15
436-99-264	Open-label, single-dose, two-period, randomized crossover, fasting bioavailability study of levothyroxine 600 µg given in 50 µg (12 tablets) versus 100 µg (6 tablets) in normal, healthy male and female volunteers.	17
436-99-277	Open-label, single-dose, two-period, randomized crossover, fasting bioavailability study of levothyroxine 600 µg given in 300 µg (2 tablets) versus 100 µg (6 tablets) in normal, healthy male and female volunteers.	19
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Background

The production of endogenous levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secretes thyroid stimulating hormone-releasing hormone (TSH-RH), which stimulates the anterior pituitary to produce thyroid stimulating-hormone (TSH). TSH then stimulates the thyroid gland to produce levothyroxine (T₄) and triiodothyronine (T₃). T₄ is subsequently converted to the highly active T₃ in the peripheral tissues. High levels of T₄ inhibit the production of TSH and to a lesser extent, TSH-RH. This effect in turn decreases the further production of T₄.

Because of the negative feedback controlled regulatory system for T₄, analysis of *in vivo* levothyroxine sodium pharmacokinetic sample data from healthy volunteers, regarding baseline-corrected vs. uncorrected approaches, is subject to several facts:

Fact A: Levothyroxine has a half-life of approximately 6 to 7 days in healthy individuals.

Fact B: Since levothyroxine enjoys such a long half-life, T₄ levels remain fairly static and are not greatly affected by circadian rhythm.

Fact C: When a hyperphysiologic dose of levothyroxine sodium is given to a healthy subject, as in the case of the BA/BE studies in this submission, and because of the exquisite sensitivity of the thyroid hormone regulatory system to subtle changes in T₄ levels, endogenous T₄ production and secretion approaches zero within 1 hour. Subsequently, as exogenous T₄ levels begin to approach normal physiologic values, endogenous production and secretion resumes.

These facts suggest that only baseline-uncorrected data be used for analysis.

Levothyroxine sodium is the synthetic sodium salt of the levo-isomer of the endogenous thyroid hormone, thyroxine (T₄). The two, levothyroxine sodium and T₄, are identical in form and function and cannot be distinguished from one another. Levothyroxine sodium is considered a narrow therapeutic range (NTR) drug and dosing must be individualized based on T₄ and thyroid stimulating hormone (TSH) levels for each patient. Therefore, levothyroxine is supplied in numerous strengths ranging from 25 mcg to 300 mcg. The average daily dose rarely exceeds 180 mcg/day. Levothyroxine sodium products have been used extensively in the clinical setting for the treatment of conditions related to thyroid hormone deficiency, thyroid nodules, and goiters.

Drug Formulation

Is the composition of each strength tablet similar?

Each strength tablet is proportionally similar in its active and inactive ingredients, but quantitatively different in the amounts of levothyroxine and lactose monohydrate, such that each tablet has a final weight of 100 mg. Genpharm levothyroxine tablets do not contain coloring agents and have a white appearance.

Components and Composition			
Component	Amount Per Tablet	Component	Amount Per Tablet
25 mcg Tablet		125 mcg Tablet	
Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.025 mg	Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.125 mg
50 mcg Tablet		137 mcg Tablet	
Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.050 mg	Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.137 mg
75 mcg Tablet		150 mcg Tablet	
Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.075 mg	Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.150 mg
88 mcg Tablet		175 mcg Tablet	
Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.088 mg	Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.175 mg
100 mcg Tablet		200 mcg Tablet	
Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.100 mg	Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.200 mg
112 mcg Tablet		300 mcg Tablet	
Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.112 mg	Levothyroxine Sodium Lactose Monohydrate Corn Starch Gelatin Croscarmellose Sodium Magnesium Stearate	0.300 mg

Dissolution

Has the sponsor proposed an appropriate dissolution method and specification?
Was sufficient data submitted for evaluation of the dissolution method and specification?

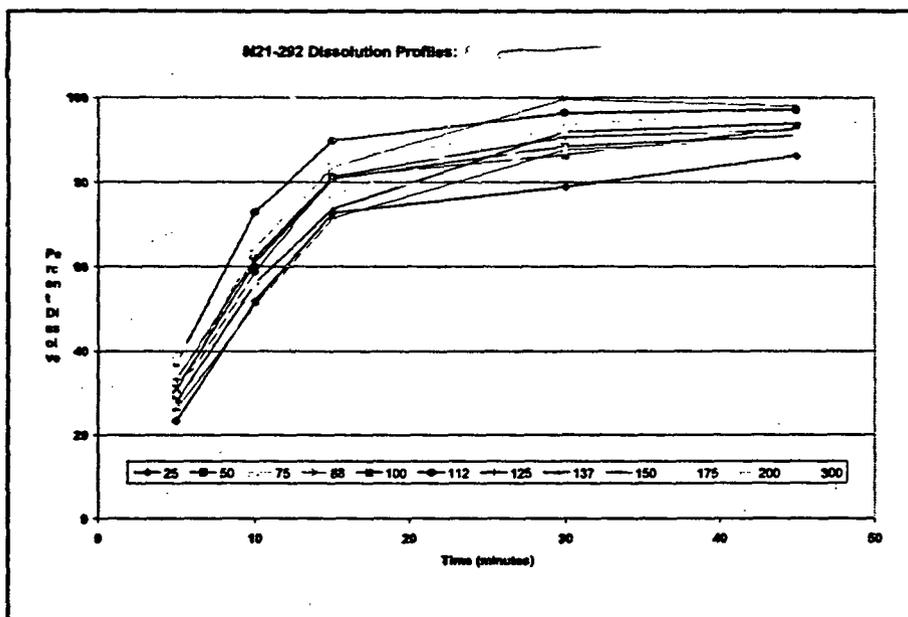
The sponsor originally proposed a single quality control dissolution method which followed the USP 23 monograph for levothyroxine sodium tablets. As the USP 23 monograph for levothyroxine sodium tablets has been updated (1-JAN-00; USP 24), it is not currently viewed as being acceptable. One of the disadvantages of using the USP 23 method is the fact that the paddle (apparatus 2) speed is designated at _____ his paddle speed is not acceptable to the Agency under most circumstances. In addition, the media consists of a _____ which the Agency views as unacceptable except in exceptional circumstances (dissolution media pH should not exceed 6.8). Because of these issues, and the fact that a new dissolution monograph exists for levothyroxine sodium, the sponsor was asked to use the USP 24 dissolution method or other method specific to their product.

Early results from the sponsor's dissolution studies indicated that the USP 24 method was unsatisfactory for day-to-day quality assurance due to a "coning" effect that occurs at low paddle speeds (i.e., 50 RPM). Therefore, despite the fact that the Genpharm levothyroxine tablets were able to meet the USP 24 tolerance specifications for levothyroxine sodium, it was not suitable for quality control. The sponsor then proceeded to develop several "in-house" methods (IHM). The final IHM, submitted on 10-APR-2001, which included multipoint dissolution profiles on all to-be-marketed strengths, utilizes a _____ media and paddle speed of _____. This method was deemed acceptable by the Agency. See *Appendix - Dissolution* for results.

In the following table, the dissolution methods researched during the genesis of this product are listed:

Dissolution Method						
Method:	USP 23	IHM	IHM-Test	USP 24	USP 24-Test	Final IHM
Apparatus:	2 (paddles)					
Speed:						
Medium:						
Volume:						
Temperature:						
pH:						
Units Tested:						
Time Points:						
Specifications:						

The following plot depicts the mean multipoint dissolution values of 12 units from each of to-be-marketed formulations using the final GenPharm in-house dissolution method.



Analytical Methodology

Have the analytical methods been sufficiently validated?

	T ₂				T ₁		
	436-99-263	436-99-264	436-99-277		436-99-263	436-99-264	436-99-277
LOQ (ng/mL):				LOQ (mcg/dL):			
Calibration (ng/mL):				Calibration (mcg/dL):			
Precision (%RSD):				Precision (%RSD):			
0.70 ng/mL				4.50 mcg/dL			
1.50 ng/mL				8.00 mcg/dL			
3.70 ng/mL				15.0 mcg/dL			
Accuracy (%):				Accuracy (%):			
0.70 ng/mL				4.50 mcg/dL			
1.50 ng/mL				8.00 mcg/dL			
3.70 ng/mL				15.0 mcg/dL			

Human Pharmacokinetics and Bioavailability Studies

1. Single-Dose Bioavailability Study

What is the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference oral solution under fasting conditions?

The relative bioavailability (F_{rel}) of levothyroxine sodium was studied in 28 healthy volunteers (24 completed study) given either a single dose of two 300 mcg tablets (lot # 007514) or a single 600 mcg dose (Levothyroxine for Injection 200 mcg, lot # 190424) of an oral solution in a two-way crossover study (436-99-263), under fasting conditions. The relative bioavailability of a single dose of two 300 mcg tablets of levothyroxine sodium, compared to an equivalent oral solution dose, was found to be approximately 99%. Results and 90% confidence intervals are presented in the following two tables:

Summary of Bioavailability Data – T ₄ Baseline Uncorrected – Study Number 436-99-263		
Parameters	Treatment A 2 x 300 mcg tablets	Treatment B 600 mcg oral solution
AUC ₀₋₄₈ (mcg*hr/dL)	483.74 ± 64.56	489.71 ± 66.12
C _{max} (mcg/dL)	13.57 ± 1.79	13.80 ± 2.13
T _{max} (hours)	2.46 ± 0.95	1.69 ± 0.79
Mean ± SD		

Least Squares Mean – 90% Confidence Interval – Study Number 436-99-263				
Treatment Comparison	Parameter	Point Estimate	CI (low)	CI (high)
A vs. B	ln C _{max}	98.58	95.36	101.90
	ln AUC ₀₋₄₈	98.78	96.76	100.85
Treatment A = 2 x 300 mcg levothyroxine tablets – Test – (%CV: C _{max} = 13.18; AUC ₀₋₄₈ = 13.35)				
Treatment B = 600 mcg levothyroxine oral solution – Reference – (%CV: C _{max} = 15.46; AUC ₀₋₄₈ = 13.50)				

2. Dosage Form Equivalence Studies

Has dosage form equivalence been established between the to-be-marketed strengths?

The sponsor submitted studies 436-99-264 and 436-99-277 to establish dosage form equivalence between the 50 mcg (lot # 007503) and 100 mcg (lot # 007502 & 007504) tablets, and 100 mcg (lot # 007504) and 300 mcg (lot # 007514) tablets, respectively. Both studies were of a two-way crossover design conducted in 24 healthy normal subjects following a 10 hour fast. Results indicate that 12 x 50 mcg and 6 x 100 mcg, and 6 x 100 mcg and 2 x 300 mcg tablets, respectively, are dosage-form equivalent. Percent coefficients of variation were consistent and 90% confidence intervals for C_{max} and AUC₀₋₄₈ parameters were within acceptable limits. Serum concentration profiles are presented in the Appendix – see Profiles.

Summary of Bioavailability Data – T ₄ Baseline Uncorrected			
Study #	Parameters	Treatment A 12 x 50 mcg tablets	Treatment B 6 x 100 mcg tablets
436-99-264	AUC ₀₋₄₈ (mcg*hr/dL)	484.58 ± 58.47	492.41 ± 75.14
	C _{max} (mcg/dL)	13.17 ± 1.92	13.74 ± 2.53
	T _{max} (hours)	2.67 ± 0.95	2.40 ± 1.14
Study #	Parameters	Treatment A 2 x 300 mcg tablets	Treatment B 6 x 100 mcg tablets
436-99-277	AUC ₀₋₄₈ (mcg*hr/dL)	503.54 ± 48.74	492.65 ± 41.24

C_{max} (mcg/dL)	13.13 ± 1.79	13.03 ± 1.36
T_{max} (hours)	2.83 ± 2.37	2.63 ± 1.34
Mean ± SD		

Least Squares Mean – 90% Confidence Interval				
Treatment Comparison	Parameter	Point Estimate	CI (low)	CI (high)
436-99-264 A vs. B	In C_{max}	96.40	92.81	100.13
	In AUC_{0-48}	98.73	96.22	101.30
436-99-277 A vs. B	In C_{max}	100.28	97.23	103.43
	In AUC_{0-48}	102.09	100.08	104.15
436-99-264 Treatment A = 12 x 50 mcg levothyroxine tablets – Test – (%CV: C_{max} = 14.56; AUC_{0-48} = 12.07) Treatment B = 6 x 100 mcg levothyroxine tablets – Reference – (%CV: C_{max} = 18.44; AUC_{0-48} = 15.26) 436-99-277 Treatment A = 2 x 300 mcg levothyroxine tablets – Test – (%CV: C_{max} = 13.62; AUC_{0-48} = 9.68) Treatment B = 6 x 100 mcg levothyroxine tablets – Reference – (%CV: C_{max} = 10.43; AUC_{0-48} = 8.37) %CV calculated from untransformed data = total variability				

In addition to analyzing the study data for all subjects, gender specific analysis was also conducted. Results of these analysis concluded that there existed a significant gender effect on PK. However, this effect has no impact on the dosage-form equivalence of this product (see *Appendix* for complete study report). The clinical result of this gender effect is not a critical issue, in that all patients must be titrated to therapeutic effect. The higher AUC values seen in females are likely due to the increased TBG levels associated with estrogen.

It should be noted, that AUC_{0-inf} is an unreliable measure of bioequivalence because it uses the values of K_e that cannot be estimated reliably using baseline-uncorrected data because the T_4 approached baseline asymptotically which overestimates the $t_{1/2}$. Therefore, AUC_{0-48} and C_{max} are the most reliable parameters for determining extent and rate of absorption and the most reliable measures of bioequivalence. For the purposes of this review, only AUC_{0-48} and C_{max} will be used for comparison.

3. Biowaivers

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

- 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.
- Each strength tablet is proportionally similar in its active and inactive ingredients.
- The final condition used to evaluate whether a biowaiver can be granted is based on the multipoint dissolution testing. F_2 calculations were 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. These three references were chosen because they were studied *in vivo* and were shown to exhibit dosage-form equivalence. Results of the curve similarity testing are presented in the following table. These results were found to be acceptable to the Agency.
 - A biowaiver can be granted for the 9 intermediate strengths not studied in the *in vivo* studies.

Reference	300 mcg		100 mcg		50 mcg	
	Strength	F_2	Strength	F_2	Strength	F_2
Test	200	75	88	60	25 mcg	57
	175	60	75	66		
	150	50				
	137	56				
	125	79				
	112	57				
Biostudy Comparison	100	76				
	50	70				

Labeling Comments

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Steven B. Johnson, B.S.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 10-JAN-2001

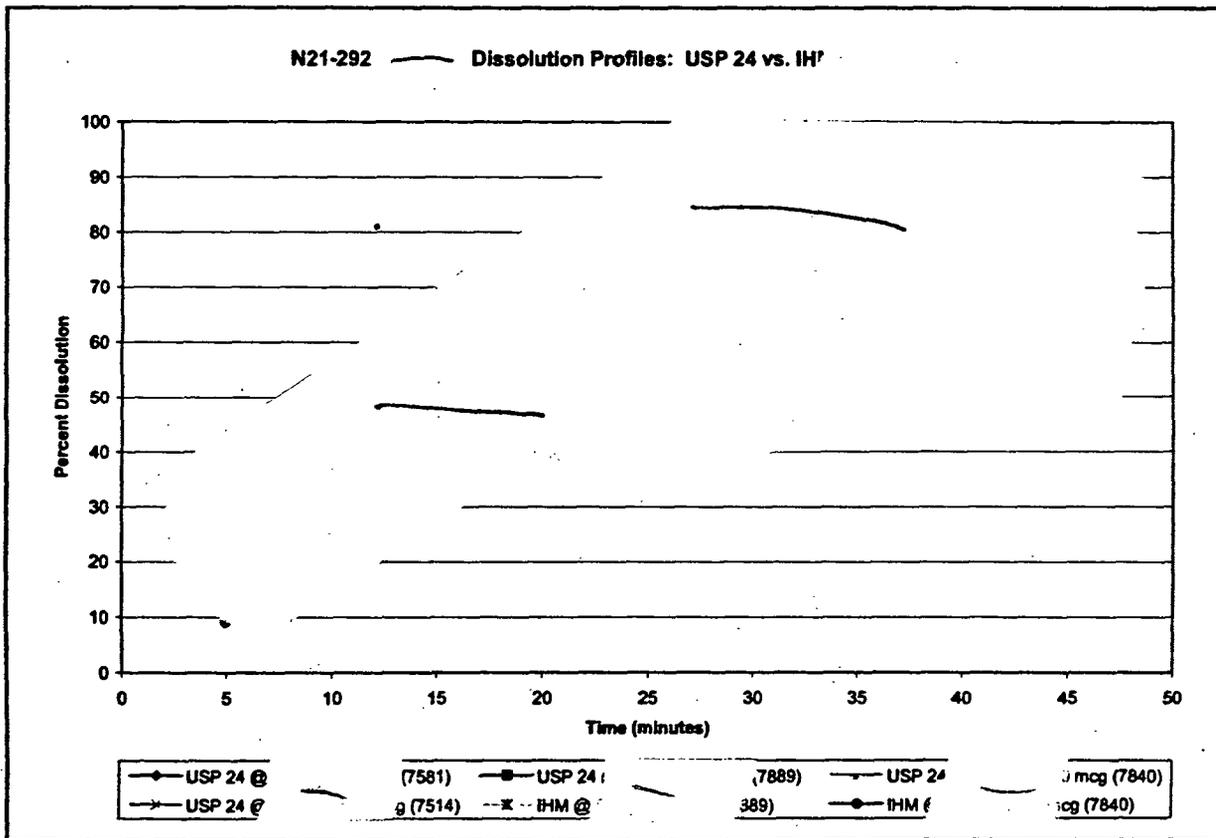
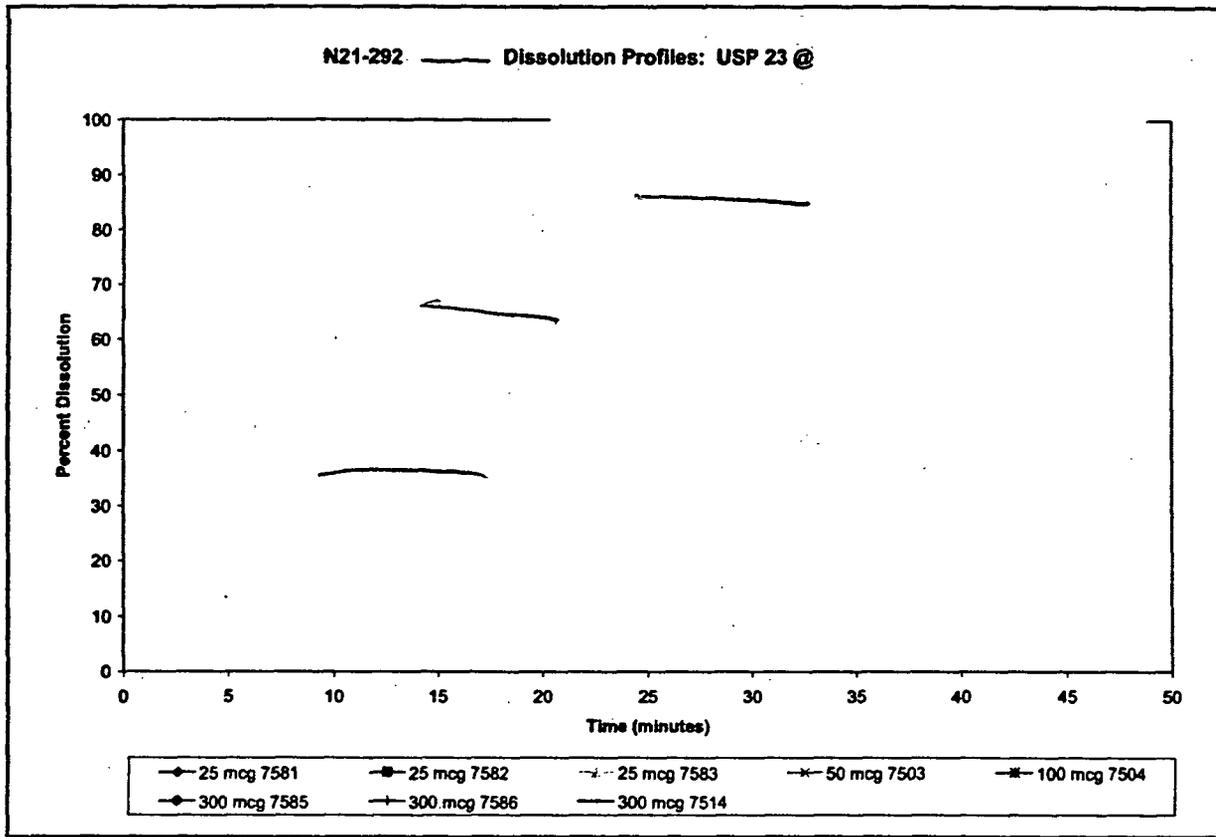
OCPB Briefing on: 30-JAN-2001

Briefing Attendees: Hank Malinowski, John Hunt, Lawrence Lesko, John Lazor, Mehul Mehta, Hae-Young Ahn, Wei Qiu, Lawrence Yu, Rabbe Patnaik, Ye-Chain Huang, Mei-Ling Chen, Larry Ouderkirk, and Chris Rogers.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: 25-APR-2001

CC: NDA 21-292 (orig., 1 copy), HFD-510 (McCortS), HFD-870 (AhnH, MalinowskiH, JohnsonST), HFD-850 (ChenME), CDR

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Tracking/Action Sheet for Formal/Informal Consults

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DATE: 9-AUG-2000

IND No.: NA
Serial No.: NA

NDA No.
21-292

Document ID:

DATE OF DOCUMENT
6-JUL-2000

NAME OF DRUG
(levothyroxine Na⁺)

PRIORITY CONSIDERATION
5S

Document Type and Sequence
No.:

Date of informal/Formal Consult:
17-JUL-2000

NAME OF THE SPONSOR: [Genpharm Incorporated]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS ASSIGNMENT

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| <input type="checkbox"/> PRE-IND | <input checked="" type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input checked="" type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input checked="" type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-
NDA/CMC/Pharmacometrics/Others) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):
[Filing Memo] |
| <input type="checkbox"/> PHASE IV RELATED | | |

REVIEW ACTION

This Application is filable – see attached memo.

NAI (No action indicated)

- | | | |
|--|--|---|
| <input type="checkbox"/> E-mail comments to:
<input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | <input type="checkbox"/> Oral communication with
Name: []
<input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes dated:
[] | <input checked="" type="checkbox"/> Formal Review/Memo (attached)
<input checked="" type="checkbox"/> See comments below
<input type="checkbox"/> See submission cover letter
<input type="checkbox"/> OTHER (SPECIFY BELOW):
[] |
|--|--|---|

REVIEW COMMENT(S)

NEED TO BE COMMUNICATED TO THE SPONSOR

HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS:

Please convey the comments to sponsor as described in the attached memo.

SIGNATURE OF REVIEWER: _____

Date _____

SIGNATURE OF TEAM LEADER: _____

Date _____

CC.: NDA 21-292, HFD-510 (McCort), HFD-870 (Huang, Ahn,
Johnson), HFD-850 (Lee), CDR

Project Manager: _____ Date _____

New Drug Application Filing Memorandum

Office of Clinical Pharmacology and Biopharmaceutics

NDA:	21-292	Priority Classification:	5S
IND:	_____	Indication:	Thyroid Replace.
Brand Name:	_____	Submission Date:	6-JUL-2000
Generic Name:	Levothyroxine Sodium	Route of Administration:	Oral, Tablets
Sponsor:	Genpharm	UFGD:	4-MAY-2000
Reviewer:	Steven B. Johnson, Pharm.D.	Review Division:	870
Team Leader:	Hae-Young Ahn, Ph.D.	Medical Division:	510
Items included in NDA (CTD)		Yes	No
Table of Contents present and sufficient to locate reports, tables, data, etc.		X	
Tabular Listing of All Human Studies		X	
HPK Summary		X	
Study Synopsis		X	
Labeling		X	
Bioavailability and Bioequivalence Studies:			
ADME Study –			X
BA Studies – Absolute BA Relative BA		X	X
BE Studies – Population BE Individual BE		X	X
Food-Drug Interaction Study			X
In Vitro-In Vivo Comparison (IVIVc) Studies			X
Reference Bioanalytical and Analytical Methods			X
Dissolution Profiles		X	Incomplete
Studies Using Human Biomaterials:			
Plasma Protein Binding Studies			X
Metabolism Studies Using Hepatocytes, Microsomes, etc.			X
Blood / Plasma Ratio			X
Human Pharmacokinetics (PK) Studies:			
PK and Initial Safety and Tolerability in <u>Healthy</u> Volunteers – Single Dose Multiple Dose			X X
PK and Initial Safety and Tolerability in <u>Patient</u> Volunteers – Single Dose Multiple Dose			X X
Dose Proportionality – Single Dose Multiple Dose			X X
PK in Population Subsets to Evaluate Intrinsic Factor Effects – Ethnicity Gender Pediatrics Geriatrics Renal Impairment Hepatic Impairment			X X X X X X
PK in Population Subsets to Evaluate Extrinsic Factor Effects – In-Vivo Effects on Primary Drug In Vivo Effects of Primary Drug			X X

In-Vitro Drug Interaction		X	
Population PK Studies		X	
Summary of PK / PD Studies		X	
PK / PD Studies in Volunteers		X	
PK / PD Studies in Patients		X	
Individual Datasets for all PK and PK / PD Studies in Electronic Format		X	
Other:			
Genotype / Phenotype Studies		X	
Chronopharmacokinetics		X	
Literature – Number of Articles Sufficient	X		
Which Phase IV Studies Requested?			
None			
Listing of Study Titles:			
436-99-263 – Open-label, single-dose, two-period, randomized crossover, fasting bioavailability study of levothyroxine 600 mcg, given in 300 mcg (2 tablets) versus an oral solution at an equivalent dose in normal, healthy male and female volunteers.			
436-99-264 – Open-label, single-dose, two-period, randomized crossover, fasting bioavailability study of levothyroxine 600 mcg, given in 50 mcg (12 tablets) versus 100 mcg (6 tablets) in normal, healthy male and female volunteers.			
436-99-277 – Open-label, single-dose, two-period, randomized crossover, fasting bioavailability study of levothyroxine 600 mcg, given in 300 mcg (2 tablets) versus 100 mcg (6 tablets) in normal, healthy male and female volunteers.			

This application is filable.

Comments to be sent to Sponsor:

I would like to send a formal memo to the sponsor that conveys the following discussion items so that my requests are properly documented in the Division files. The three items listed below were discussed in a telephone conference with Tirtho Uppal, Director of Regulatory Affairs for Genpharm, on Friday, August 11, 2000. She was made aware that these items should be addressed in an amendment to the application.

1. The use of the dissolution method as described in the USP 23 monograph for levothyroxine sodium tablets is not current nor is it acceptable to the Agency. Please refer to the current USP 24 monograph for levothyroxine sodium tablets for the revised compendial dissolution method.
2. In order to grant a biowaiver for the intermediate strength tablets not evaluated in the PK studies, dissolution data must be submitted for at least three lots of each to-be-marketed strength tablet (3 x 12 strengths = 36 tests); which is to include those lots used in the PK studies, using the revised dissolution method.
3. Similarity (f_2) calculations will be based on the following criteria: 300 mcg tablets will serve as the reference for the 112 mcg through 200 mcg strengths; 100 mcg tablets will serve as the reference for the 75 mcg and 88 mcg strengths; and the 50 mcg tablets will serve as the reference for the 25 mcg strength.

**APPEARS THIS WAY
ON ORIGINAL**