CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-342

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

Information		Information	
NDA Number:	21-342	Brand Name:	LEVO-T
OCPB Division (I, II, III):	DPE-II (HFD-870)	Generic Name:	Levothyroxine Sodium
Clinical Division:	DMEDP (HFD-510)	Drug Class:	Synthetic thyroxine
CPB Reviewer:	Steven B. Johnson, Pharm.D.	Indication(s):	Thyroid hormone replacement
CPB Team Leader:	Hae-Young Ahn, Ph.D.	Dosage Form:	Tablet
Submission Date:	30-APR-2001	Dosing Regimen:	QD (once daily)
PDUFA Date:	01-MAR-2002	Route of Administration:	PO (oral)
Priority Classification:	Standard	Sponsor:	Mova Pharmaceuticals Corp.

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:				
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			
Other Formulation as Reference:				
Bioequivalence Studies –				
– Traditional Design –				
Single-Dose:	X			
Multiple-Dose:				

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– Replicate Design –				
Single-Dose:				
Multiple-Dose:				
Food-Drug Interaction Studies:				
Dissolution:	X			
In-vitro/In-vivo Correlation:				
BCS Based Biowaiver Request:				
BCS Classification Information:				
III. Other CPB Studies				
Genotype / Phenotype Studies:				
Chronopharmacokinetics:				
Pediatric Development Plan:				
Literature References:				
[redacted]	[redacted]			

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
990673	Comparative, randomized, 2-way crossover bioavailability study of Mova 300 mcg levothyroxine sodium tablets and Knoll (SYNTHROID™) 200 mcg vials of levothyroxine sodium injection (taken orally) in healthy adult males and females, following administration of a 600 mcg dose under fasting conditions.
990675	Comparative, randomized, 3-way crossover dosage form equivalence study of Mova 50 mcg, 100 mcg, and 300 mcg levothyroxine sodium tablets, following administration of a 600 mcg doses, in healthy adult males and females under fasting conditions.

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NDA #:	21-342	**RELEVANT IND #:**	———
BRAND NAME:	LEVO-T™	**GENERIC NAME:**	Levothyroxine Sodium
STRENGTH(S):	0.025, 0.050, 0.075, 0.088, 0.100, 0.112, 0.125, 0.150, 0.175, 0.200, & 0.300 mg		
DOSAGE FORM:	Tablet		
APPLICANT:	Mova Pharmaceuticals Corporation Villa Blanca Industrial Park, State Road #1 Km 34.8, Jose' Garrido Avenue, Cagulas, P.R. 00725		
LETTER DATE:	30-APR-2001	**PDUFA DATE:**	01-MAR-2002
OCPB DIVISION:	DPE-II	**ORM DIVISION:**	DMEDP
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

Executive Summary

Mova Pharmaceutical Corporation has submitted NDA 21-342 for LEVO-T™ Brand of levothyroxine sodium tablets. This application contained two clinical pharmacokinetics studies and relevant dissolution information for review. Of the two studies submitted, one was a relative bioavailability study that compared 2 x 300 mcg tablets with a 600 mcg oral solution, and the other was a dosage-form proportionality study that compared 50 mcg and 300 mcg tablets with the 100 mcg tablets, respectively. The dissolution method that was used for LEVO-T™ followed the method outlined in the USP 24 Supplement 1 monograph for levothyroxine sodium tablets. This method is acceptable to the Agency and is discussed under the Dissolution section of this review.

The relative bioavailability study, 990673, 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 LEVO-T™ 300 mcg tablets is approximately 99%. Both AUC_{0-48} and C_{max} were comparable between formulations. However, T_{max} was expectedly prolonged when subjects were administered the tablet formulation (3.6 vs. 2.5 hours).

The dosage-form proportionality study, 990675, compared a single dose of twelve 50 mcg or two 300 mcg tablets with a single dose of six 100 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 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, despite following the compendial guidelines, yielded results that exhibited considerable intra- and inter-lot variability. This variability was primarily attributed to two sources: 1) a particular lot series (i.e., YT340 – YT344); and 2) assay or technical error – testing conducted in March, 2000, resulted in an approximate 15% difference from later results, and there was an adsorption problem with later sampling time points. As a result, the sponsor was asked to submit new multipoint dissolution profile data from a single lot of each to-be-marketed strength, separate single-point dissolution data at a 15-minute time point, and multipoint dissolution profile data for the 300 mcg tablet strength without surfactant at paddle speeds of 50 and 75 RPMs.

Results of the requested dissolution data continued to indicate that technical error was still occurring. An example of this error was evident with the 75 mcg and 125 mcg strengths. In both cases, previous dissolution data indicated that by the 15 minute sampling point, there was ——— dissolution. However, in the Agency requested data, the values were 15%–10% lower – corresponding %CV were 3.7 and 2.5, respectively. Additionally, the multipoint dissolution data using media without SLS suggested that incomplete dissolution occurs and the use of SLS in the dissolution media is justified. Given the multi- and single-point dissolution data presented in this application, a dissolution tolerance specification of ——— (Q) @ 15 minutes has been selected.

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* should be granted.

The DSI audit was scheduled to begin on 28-JAN-2002 – results of the audit will be available prior to the PDUFA action date.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-342 for LEVO-T™ brand of levothyroxine sodium tablets and finds the results presented in this application acceptable. However, final judgement is reserved until the results from the pending DSI audit are made available to this reviewer.

Comments to Sponsor

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed Section 6 of NDA 21-342 for LEVO-T™ brand of levothyroxine sodium tablets and has set the dissolution method and tolerance specifications as follows:

Apparatus Type	2 (paddles)
Media	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume	500 mL
Speed of Rotation	50 RPM
Tolerance Specifications	**NLT ——(Q) of the labeled amount of levothyroxine sodium is dissolved in 15 minutes**

Although the Agency was able to set a dissolution tolerance specification for LEVO-T™, the results of the dissolution studies indicated a great deal variability. Please submit a report to the Agency to explain why some of your dissolution data exhibit values that are considerably greater than 100%, why 2 significantly different dissolution values are reported for the same strength on the same day, and why the calibration/standard curve from your Quality Control laboratory did not appear linear.

Phase IV Commitments

NONE

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Summary of CPB Findings

- Each of the 11 tablet strengths of LEVO-T™ was found to be proportionally similar in formulation;
- The dissolution method [and specifications] were determined to be appropriate for LEVO-T™;
- The bioavailability of LEVO-T™, relative to an equivalent oral solution, was 99%;
- 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 not studied *in vivo*.

Chemistry

Is the formulation for LEVO-T™ proportional, by CFR definition, between strengths?

The formulation for LEVO-T™ does exhibit proportionality between strengths. The only differences between the strengths is the amount of active ingredient [redacted], levothyroxine sodium [redacted]

Table 1: LEVO-T™ Formulation

Component	Reference	25	50	75	88	100	112
Levothyroxine sodium	USP	0.025	0.050	0.0750	0.0880	0.100	0.1120
Sodium starch glycolate	NF	[redacted]					
[redacted]	[redacted]						
Magnesium stearate	NF						
FD&C Yellow #6 Al Lake	21 CFR[3]						
FD&C Blue #2 Al Lake	21 CFR[4]						
FD&C Red #40 Al Lake	21 CFR[5]						
D&C Yellow #10 Al Lake	21 CFR[6]						
FD&C Blue #1 Al Lake	21 CFR[7]						
D&C Red #30 Al Lake	21 CFR[8]						
D&C Red Lake Blend	21 CFR[9]						
D&C Red #27 Al Lake	21 CFR[10]						
Total Weight		[redacted]					

Component	Reference	125	150	175	200	300
Levothyroxine sodium	USP	0.125	0.150	0.175	0.200	0.300
Sodium starch glycolate	NF	[redacted]				
[redacted]	[redacted]					
Magnesium stearate	NF					
FD&C Yellow #6 Al Lake	21 CFR[3]					
FD&C Blue #2 Al Lake	21 CFR[4]					
FD&C Red #40 Al Lake	21 CFR[5]					
D&C Yellow #10 Al Lake	21 CFR[6]					
FD&C Blue #1 Al Lake	21 CFR[7]					
D&C Red #30 Al Lake	21 CFR[8]					
D&C Red Lake Blend	21 CFR[9]					
D&C Red #27 Al Lake	21 CFR[10]					
Total Weight		[redacted]				

[redacted]

[3] 21 CFR 82.51, 82.706, 74.1706
[4] 21 CFR 82.51, 74.1102
[5] 21 CFR 74.1340, 82.51
[6] 21 CFR 74.1710, 82.1051, 82.1710
[7] 21 CFR 74.1101, 82.51, 82.101
[8] 21 CFR 74.1330, 82.1051
[9] 21 CFR 74.1330, 82.1051, 74.1327
[10] 21 CFR 74.1327, 82.1051

Dissolution

Is the dissolution method and tolerance specification appropriate for LEVO-T™ tablets?

At the request of the Office of Clinical Pharmacology and Biopharmaceutics, the sponsor has submitted multipoint dissolution profiles on three lots of each to-be-marketed tablet strength using the dissolution method outlined in the USP 24 Supplement 1 monograph for levothyroxine sodium tablets (see ***TABLE 2***).

TABLE 2: USP 24 Supplement 1 Dissolution Method for Levothyroxine Sodium Tablets	
Apparatus Type	2 (paddles)
Media	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume	500 mL
Speed of Rotation	50 RPM
Sampling Times	10, 20, 30, and 45 minutes
Tolerance Specifications	NLT — (Q) of the labeled amount of levothyroxine sodium is dissolved in — minutes

Results of this dissolution study showed that LEVO-T™ tablets dissolve rapidly. However, despite this rapid dissolution, several strengths demonstrate considerable intra- and inter-lot variability – some inter-lot profiles differ by as much as 20% (see ***TABLE 3 & PLOT 1***). This presents a dilemma in evaluating and setting the tolerance specifications for LEVO-T™. As such, the sponsor was asked to submit additional dissolution data on a single lot of each to-be-marketed strength, 6 units per strength, using sampling time points of 5, 10, 15, and 20 minutes. There also appears to be an inherent problem with the assay that results in declining values with later time points – we believe this to be related to the adsorption of levothyroxine to some component of the HPLC itself. To confirm this belief, the sponsor was also asked to submit single point dissolution data on each of the to-be-marketed strengths at the 15 minute time point. In addition, due to the rapid rate of dissolution with a media that contains sodium lauryl sulfate (SLS), the sponsor was asked to submit data on a single strength using non-SLS media at different paddle speeds. This additional data is presented in ***TABLES 4 & 5, and PLOTS 1 & 2***.

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

	25 mcg			50 mcg			75 mcg			88 mcg			100 mcg			112 mcg		
Time	YT032E	YT033E	YT034E	YT192E	YT305E	YT339E	YT200E	YT201E	YT202E	YT214E	YT215E	YT340E	YT038E	YT050E	YT341E	YT196E	YT273E	YT342E
10	97	79	99	95	97	90	89	83	79	90	95	90	[illegible]	92	77	95	96	81
20	109	93	106	101	104	90	93	89	81	98	99	98	[illegible]	97	86	98	100	86
30	108	98	104	100	104	86	95	89	82	98	99	103	[illegible]	96	89	100	100	87
45	107	99	105	100	104	83	95	91	84	99	100	100	[illegible]	96	88	101	100	85

	125 mcg			150 mcg			175 mcg			200 mcg			300 mcg		
Time	YT211E	YT212E	YT343E	YT204E	YT205E	YT206E	YT194E	YT195E	YT344E	YT207E	YT208E	YT209E	YT036E	YT037E	YT038E
10	90	89	90	96	86	95	86	72	75	86	89	93	92	93	[illegible]
20	99	95	95	101	94	99	96	81	86	95	96	99	98	100	[illegible]
30	100	96	94	102	96	99	98	86	88	97	98	101	99	100	[illegible]
45	101	97	94	103	95	100	98	89	90	97	99	101	99	99	[illegible]

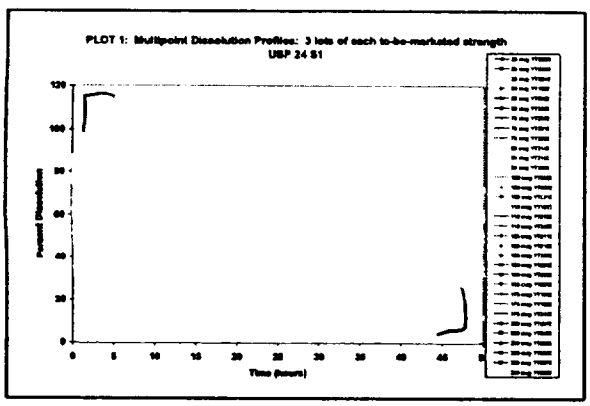
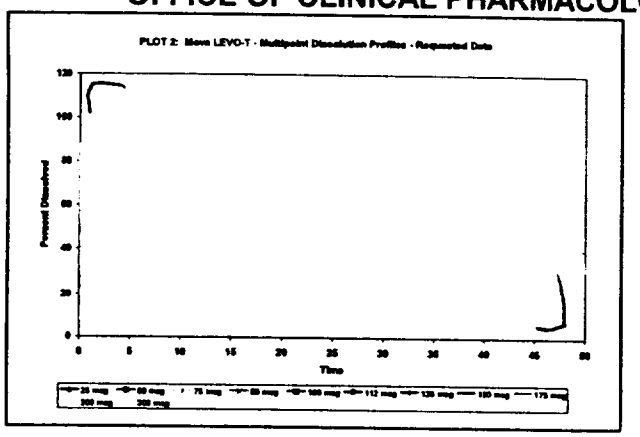
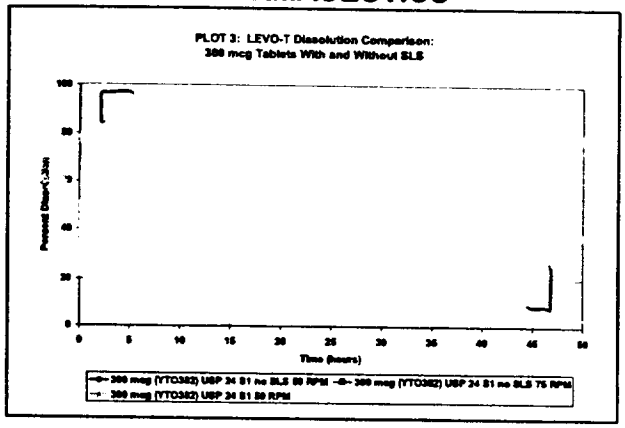


TABLE 4: Multipoint dissolution profiles - USP 24 S1 - Agency requested data (n = 6 units)											
	25 mcg	50 mcg	75 mcg	88 mcg	100 mcg	112 mcg	125 mcg	150 mcg	175 mcg	200 mcg	300 mcg
Time	YT0332	YT3393	YT2001	YT3403	YT3412	YT3423	YT3433	YT2043	YT1953	YT2073	YT0382
5	81	97	82	98	78	83	67	86	74	75	74
10	96	101	86	109	84	90	75	94	83	85	85
15	98	106	88	110	90	94	77	98	90	90	90
20	101	104	88	112	92	96	80	100	92	93	92

TABLE 5: Single Point Dissolution Data: USP 24 S1 @ 15 minutes											
	25 mcg	50 mcg	75 mcg	88 mcg	100 mcg	112 mcg	125 mcg	150 mcg	175 mcg	200 mcg	300 mcg
Time	YT0332	YT3393	YT2001	YT3403	YT3412	YT3423	YT3433	YT2043	YT1953	YT2073	YT0382
15	89	96	[illegible]	92	91	90	88	92	89	94	90





Results of the Agency requested data continue to indicate an error in the dissolution technique. However, despite this error, sufficient data has been submitted to justify setting a dissolution tolerance specification of —— (Q) @ 15 minutes. The data also suggests that the use of SLS in the dissolution media is justified, despite the rapid dissolution rate of this product.

NOTE: A telephone conference between this reviewer and Aracelis Ramirez, Mova Pharmaceuticals Quality and Regulatory Affairs Vice President, was held on 28-JAN-2002 to discuss an apparent discrepancy between the lot numbering schemes submitted for the dissolution and bioavailability studies.

General Biopharmaceutics

What is the bioavailability of LEVO-T™ tablets relative to an equivalent dose of an oral solution?

To determine the relative bioavailability of LEVO-T™ tablets with an equivalent dose of an oral solution, a randomized, open-label, two-way crossover study in 24 healthy male and female volunteers was conducted. Treatments consisted of administering either (Tx A) 2 x 300 mcg LEVO-T™ tablets (lot #s: YTO381 & YTO382) or (Tx B) a 600 mcg oral solution following a 10-hour fast. Results indicate that the relative bioavailability of LEVO-T™ tablets with an oral solution is **99%** (see ***TABLE 6*** and ***PLOT 4***).

Table 6: Relative bioavailability of LEVO-T tablets versus an equivalent oral solution (600 mcg)

Parameter	Unit	TX A (2 x 300 mcg tabs)	Tx B (600 mcg sln)	Point Estimate (%)	90% Confidence Intervals	
					Low	High
AUC_{0-48}	ng*hr/mL	5680.1 ± 723.47	5741.8 ± 861.39	99.0	96.3	101.8
C_{max}	ng/mL	152.15 ± 24.91	155.42 ± 26.93	97.9	93.7	102.3
T_{max}	h	3.56 ± 4.59	2.52 ± 2.32	–	–	–
Mean ± SD						

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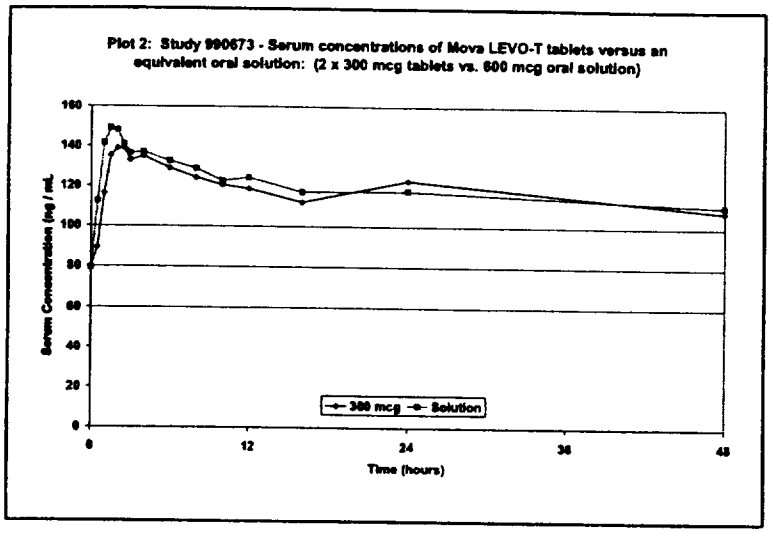

Were representative strength brackets found to be dosage-form equivalent?

Study 990675 examined the strength proportionality issue in an open-label, randomized, three-period crossover study in 24 healthy male and female volunteers under fasting conditions. Treatments consisted of either (A) 12 x 50 mcg tablets (lot #s: YTO351 & YTO352), (B) 6 x 100 mcg tablets (lot #s: YTO391 & YTO392), or (C) 2 x 300 mcg tablets (see ***TABLE 7*** and ***PLOT 5***). Analysis of the data was conducted using analysis of variance with model terms sequence, subject nested within sequence, period, and treatment. Results of this study demonstrated that 50 mcg, 100 mcg, and 300 mcg strength tablets were dosage-form equivalent for both AUC_{0-t} and C_{max}. T_{max} was also found to be similar between these three strengths (see ***TABLE 8***).

Table 7: Dosage-form equivalence of LEVO-T™ 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}	ng*hr/mL	6019.6 ± 854.33	5955.7 ± 883.36	6030.3 ± 950.38
C_{max}	ng/mL	156.80 ± 22.78	154.07 ± 20.14	157.53 ± 23.25
T_{max}	h	2.27 ± 1.25	2.54 ± 1.28	2.83 ± 1.75
Mean ± SD				

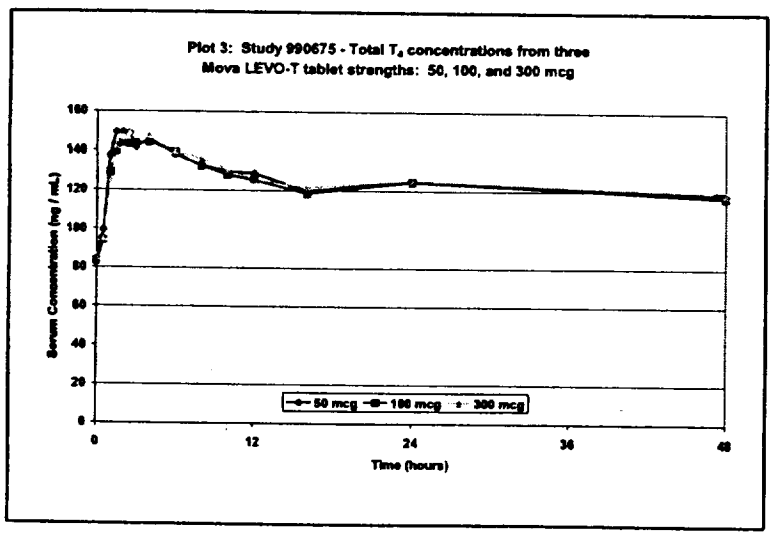

Table 8: Dosage-form equivalence of LEVO-T™ tablets at equivalent doses (600 mcg)						
Paramater	AUC_{0-48}			C_{max}		
	PE (%)	90% Confidence Intervals		PE (%)	90% Confidence Intervals	
		Low	High		Low	High
Tx A vs. Tx B	101.5	99.0	104.2	102.1	98.5	105.9
Tx A vs. Tx C	100.0	97.5	102.6	99.5	96.0	103.2
Tx B vs. Tx C	98.5	96.0	101.0	97.4	94.0	101.0

NOTE: A comparison of the T_{max} from treatment A in study 990673 and treatment C in study 990675, shows an approximate 45 minute difference, 3.56 vs. 2.83, respectively. This discrepancy was due to a single subject in 990673 that did not reach C_{max} until 24 hours after the initial dosing – hence skewing the mean. Removing this subject's data from the relative bioavailability calculation does not result in any appreciable change.

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 the multipoint dissolution testing. Normally, 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, in this case, since the LEVO-T™ product exhibits such rapid dissolution, it is assumed that the products are similar and will provide a respective strength bioavailability.

- A biowaiver can be granted for the 8 intermediate strengths not studied in the *in vivo* studies.

Analytical

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Steve Johnson
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2/12/02 02:30:41 PM
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