CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-151

BIOEQUIVALENCE REVIEW(S)

Diltiazem Hydrochloride, USP

ER capsules, 300 mg, 240 mg, 180 mg and 120 mg
ANDA # 76-151
Reviewer: Gur J.P. Singh
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TorPharm

50 Steinway Blvd
Etobicoke, Ont. M9W 6Y3
Submission Date:
August 29, 2001

Review of three bioequivalence studies, four dissolution data-sets and three waiver requests

The sponsor has submitted single dose bioequivalence studies conducted under fasting and non-fasting conditions, and a multiple dose study on its diltiazem hydrochloride 300-mg capsule. The application also contains dissolution data for these drug products., and a request for waivers of in vivo bioequivalence study requirements for the 240-mg, 180-mg and 120-mg extended release capsules.

It is noted that the sponsor already markets diltiazem hydrochloride extended release 120-mg, 180-mg and 240-mg capsules. However, those products were approved as generic versions of Dilacor® XR capsules manufactured by Watson Laboratories, not Cardizem® extended release capsules manufactured by Aventis.

Reference Listed Drug

Drug Product:	Cardizem® CD 300-mg, 240-mg, 180-mg and 120-mg extended release capsules manufactured by Aventis.
Indication:	Treatment of hypertension.
Bioavailability:	Approximately 40% following oral administration.
Metabolites:	Extensive metabolism, only 2-4% of unchanged drug appears in the urine. Desmethyl-diltiazem is approximately 20-30% as active as the parent drug, whereas diacetyl-diltiazem is approximately 50% as potent as the parent drug for coronary vasodilatation. Plasma concentrations of the parent drug and these metabolites occur in the order of parent drug> desmethyl-diltiazem > diacetyl-diltiazem.
Half Life:	2-5 hours for diltiazem.
T_{max}:	6-8 hours
Food Effect:	Food may influence the rate of absorption absorption.
DBE guidance:	No guidance specifically for diltiazem extended release capsules. However, the CDER guidance *for Bioavailability and Bioequivalence : General Consideration* is applicable.

Single-dose Fasting Bioequivalence Study on the 8-mg capsule (#2503)

OBJECTIVE: The purpose of this study was to establish bioequivalence of TorPharm's diltiazem hydrochloride 300 mg extended release capsules to Aventis 's Cardizem® CD 300 mg extended release capsules.

STUDY SITE, INVESTIGATORS AND DATES:

Clinical study site:	[redacted]
Analytical Study Site:	[redacted]
Medical Director:	[redacted]
Analytical Director:	[redacted]
Study Protocol:	Protocol (#002305, September 7, 2000, PP 1061, vol. 1.4) was approved by the [redacted] Review Board.
Dosing Dates:	September 16 and 23, 2000
Analytical Dates:	October 2 - 26, 2000

SUBJECT SELECTION:

Thirty two (32) healthy *male* volunteers were enrolled for this study. The mean age and weight of these volunteers were 31.8 years and 73.11 kg. (range (110-181), respectively (pp. 1404, vol. 1.4). Five volunteers' age were in the 40-64 years range , the remaining were in the range of 18-40 years. Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection criteria stated in the study protocol.

STUDY DESIGN: The clinical study was conducted as a single dose, randomized, two-treatment, two-period crossover evaluation with a washout period of 7 days between the two dosing days.

TREATMENTS:

A: Diltiazem hydrochloride extended release capsules 1x300 mg, TorPharm , Lot #: FDA0118A, Lot Size: [redacted] Content uniformity: 99.7%, Potency 98.1% (vol. 1.15).

B: Cardizem® CD extended release capsules 1x300 mg, Aventis , Lot #: 1009408, Lot Size: Commercial lot, Expiry Date - July 2001, Content uniformity: 99.3%, Potency 101.4% (vol. 1.15).

The randomization sequence used in the study is given in the table 2 (attachment).

DOSING:

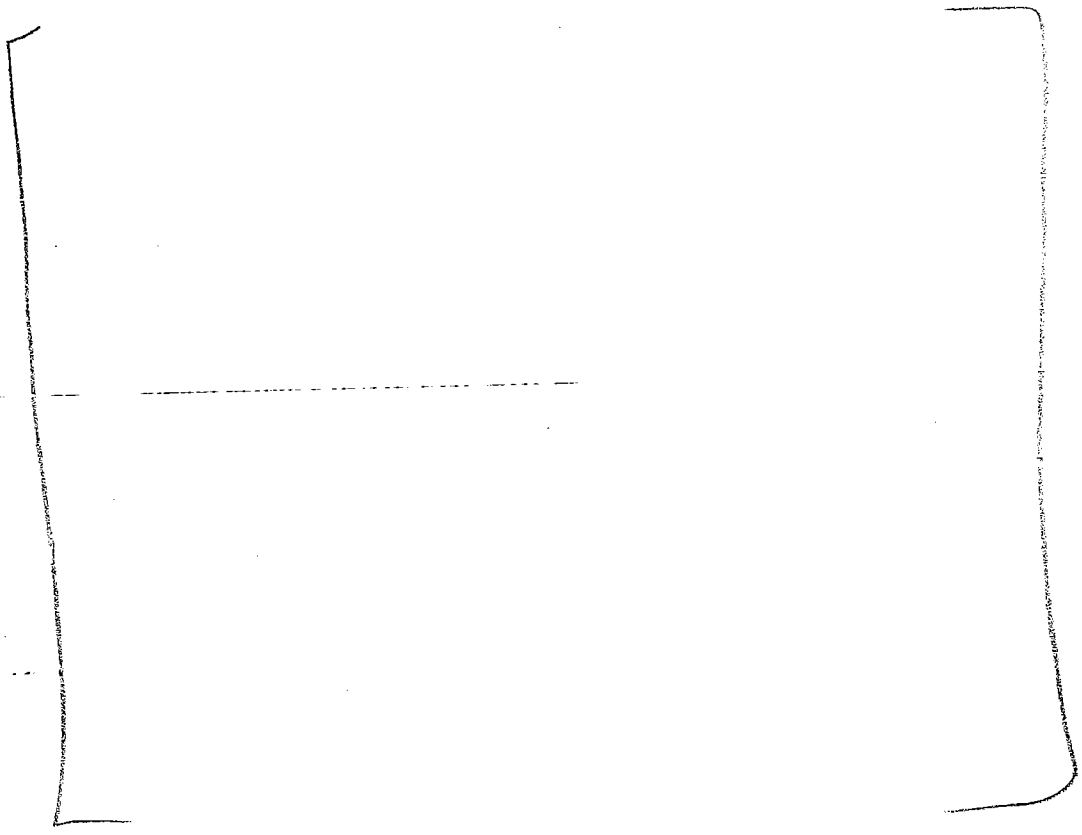
After an overnight (10 hours) fast, each drug was given orally with 240 mL of water. Within one hour before and one hour after dosing, the only water supplied was with drug administration. Subjects were confined to the clinical facility until 24 hours after dosing. They returned for subsequent blood samples.

SAMPLE COLLECTION AND STORAGE:

Sample:	Venous blood (10 mL each) collected in EDTA-containing Vacutainer® tubes.
Sampling times:	0 (pre-dose), and 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 48 and 60 hours post-dose (20 samples).
Sample Storage:	Plasma was separated and stored at $-22 \pm 10^{o}C$ until analysis.

HEMODYNAMIC EVALUATIONS: Hemodynamic measurements were taken immediately before and 6, 12 and 48 hours after dosing.

ANALYTICAL PROCEDURE (Not to be released under FOI): `



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Repeat Assays: Information regarding repeat assays is given in volume 1.8 (appendix VIII). 11.5% of total samples were reanalyzed. None of the samples was analyzed for pharmacokinetic anomalies. Repeat-assay values were reported for most samples.

Analytical Method Deficiencies: None

PHARMACOKINETIC (PK) DATA ANALYSIS:

PK Parameters: Area under the plasma concentration vs. time curve from time zero to the last quantifiable data point (AUC), $AUC_{0\text{-infinity}}$ (AUCI), C_{max}, T_{max}, elimination $t_{1/2}$ and K_{el} were computed. Parameter values were calculated for diltiazem and desmethyl-diltiazem. The reviewer has verified the AUC and AUCI values. Parametric data submitted by the firm were considered to be accurate and used by the reviewer for all statistical analyses.

Statistical analyses: The reviewer performed the analysis of variance (ANOVA) with subjects, period and treatment as factors, and sequence as between subject factor was applied to PK parameters. Statistical analyses of pharmacokinetic data were conducted using the t-test method to determine differences between diltiazem hydrochloride formulations in AUC, AUCI and C_{max} at $\propto = 0.05$ and $ß = 0.20$.

RESULTS:

Clinical Study Conduct:

Number of subject dosed:	32
Number of subjects completing the study:	29 (Subjects #13 was withdrawn due an abnormal ECG in period 1. Subject #24 withdrew from the study before the beginning of period II due to personal reasons. Subject #28 was withdrawn from the study due vomiting.
Adverse events:	Twenty five (16-test, 9-ref) adverse events possibly related to treatments were reported in this study (pp. 1409-111, vol. 1.4).
Protocol deviations:	Deviation related blood draw times of up to 16 minutes were reported. In the reviewer's opinion, these deviations should not influence the bioavailability comparisons.

PK Data:

Individual-subject plasma concentration data: Diltiazem hydrochloride plasma concentration data are given on pages 1128-1186 (vol. 1.4). Line graphs depicting individual-subject concentration vs. time profiles are also presented on the same pages Desmethyl-diltiazem plasma concentrations and line graphs are given on pages 1187-1265. The slope and intercept values, and time points for calculation of diltiazem and desmethyl-diltiazem hydrochloride Kel values are listed pages mentioned above. The sampling times represent the terminal elimination phases of the analyte profile and Kel values were determined with $r^2 \geq 0.98$.

Mean plasma concentration profiles: See tables 1 and 4 (attachment).

AUC, AUCI and C_{max} data: See table s 2 and 5 (attachment) for individual subject values, AUC/AUCI ratios and Test/Reference ratios of AUC, AUCI and C_{max}.

Bioequivalence Evaluation: Bioequivalence evaluation is based on 29 subjects' data.

Mean parametric values and test/ref ratios: see tables 3 and 6 (attachment).

90% confidence intervals: The 90% confidence intervals for AUC, AUCI and C_{max} were within the acceptable limit of 80-125% (tables 5 and 6, attachment).

Sequence Effect: Not detected based on reviewer's analyses.

Deficiencies in the fasting bioequivalence study: None

Non-fasting Bioavailability Study (Study #276-43)

OBJECTIVE: The purpose of this study was to compare post-prandial bioavailability of TorPharm's diltiazem hydrochloride 300-mg extended release capsules to that of Aventis 's Cardizem CD® 300-mg extended release capsules.

STUDY SITE, INVESTIGATORS AND DATES:

Clinical study site, Analytical Study Site: [redacted]
Medical Director: [redacted]
Analytical Director: [redacted]

Study Protocol: Protocol (#276-43, August 8, 2000, pp. 228-248, vol. 1.2) was approved by the [redacted] Review Board.

Dosing Dates: August 20, 27 and September 3, 2000.

Analytical Dates: September 12-October 3, 2000.

SUBJECT SELECTION:

Eighteen (18) healthy volunteers were enrolled for this study. The mean age and weight of these volunteers were 40 years and 75 kg, respectively. Of the eighteen subjects, eight were in age range of 10-40 years, the remaining subjects were in the range of 40-53 years. Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection stated in the study protocol.

STUDY DESIGN: The clinical study was conducted as a single dose, randomized, three-treatment, three-period crossover evaluation with a washout period of 7 days between the successive dosing days.

TREATMENTS:

A: Diltiazem hydrochloride extended release capsules 1x300 mg, TorPharm, Lot #: FDO11A8, administered following consumption of a standardized breakfast.

B: Cardizem® CD extended release capsules 1x300 mg, Aventis , Lot #: 1009408, administered following consumption of a standardized breakfast.

C: Diltiazem hydrochloride extended release capsules 1x300 mg, TorPharm, Lot #: FDO11A8, administered following an overnight fast.

The randomization code used in the study is given in the table 8 (attachment).

DOSING AND MEALS:

Each drug was given orally with 240 mL of water. The breakfast served before administration of treatments A and B included one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, 2 ounces of hash brown potatoes, six fluid ounces of orange juice, eight fluid ounces of whole milk.

SAMPLE COLLECTION AND STORAGE AND HEMODYNAMIC EVALUATIONS: Same as mentioned for the fasting study, with the exception that blood samples were collected up to 54 hours.

ANALYTICAL PROCEDURE: Same as mentioned for the fasting study.

Calibration Standards' (CS) and Quality Control (QC) samples' concentrations: Same as mentioned for the fasting study.

Specificity, Limit of Quantitation, Recovery and Stability: Same as mentioned for the fasting study. Representative chromatograms are given in volume 1.2.

Linearity: Calibration curves were linear in the range of calibration standards used (—— pp589-591, vol. 1.2).

Inter-day (Within the sample analysis period) Reproducibility and Accuracy :

	Precision	Accuracy
Diltiazem		
Based on CS:	[redacted]	[redacted]
Based on QC samples:		
Desmethyl-diltiazem		
Based on CS:		
Based on QC samples:		

(Individual run data are given on pages 589-593, vol. 1.2)

Repeat Assays: Information regarding repeat assays is given on pages 600-606, vol. 1.2. Based on reviewer's survey of these data, approximately 12% of total samples were re-analyzed for a variety of reasons. None of the samples were analyzed for pharmacokinetic anomalies. Repeat-assay values were reported for most samples.

Analytical Method Deficiencies: None

PHARMACOKINETIC (PK) DATA ANALYSIS:

PK Parameters: AUC_{0-t} (AUC), $AUC_{0-infinity}$ (AUCI), C_{max}, T_{max}, elimination $t_{1/2}$ and K_{el} were computed.

RESULTS:

Clinical Study Conduct:

Number of subject dosed: 18

Number of subjects completing the study:	17, subject #1 was withdrawn due to positive cocaine test during period 3 drug screen.
Adverse events:	Four (4) treatment-related adverse events were reported (TRT A-1, TRT B-2, TRT C-1).
Protocol deviations:	Incidences of minor deviations from scheduled blood sampling times were reported (pp. 401, vol. 1.2). In reviewer's opinion, these deviations should not affect bioavailability comparisons.

PK Data:

Individual-subject plasma concentration data: Diltiazem plasma concentration data are given on pages 286-291(vol. 1.2) . Line graphs depicting individual-subject concentration vs. time profiles are given on pages 332-338. Desmethyl-diltiazem plasma concentration data are given on pages 305-309, and its line graphs depicting individual-subject concentration vs. time profiles are given on pages 340-357. The time points for calculation of diltiazem and desmethyl-diltiazem Kel values are listed on 303 and 321 respectively (vol. 1.2). The Kel values were computed over the range of 24-54 hours, with r^2 values ——

Mean plasma concentration profiles: See tables 7 and 10 (attachment).

AUC, AUCI and C_{max} data: See tables 8 and 11 (attachment) for individual subject values, AUC/AUCI ratios and Test/Reference ratios of AUC, AUCI and C_{max}.

Bioavailability Comparisons::

Mean parametric values and test/ref ratios: see tables 9 and 12 (attachment). The test product's mean AUC, AUCI and C_{max} values were within 80-125% of those of the reference product values.

Deficiencies in the non-fasting study: None

Multiple-dose (Steady-State) Bioequivalence Study (#002872)

OBJECTIVE: The purpose of this study was to establish steady-state bioequivalence of TorPharm's diltiazem hydrochloride 300-mg extended release capsules to Cardizem® CD 300-mg extended release capsules.

STUDY SITE, INVESTIGATORS AND DATES:

Clinical and Analytical Study Sites: Same as the single dose fasting study.

Medical Director: [redacted]
Analytical Director: [redacted]

Study Protocol: Protocol (#002872, November 9, 2000, pp.3070-87, vol. 1.9) was approved by the [redacted] Review Board.

Dosing Dates: November 20-24 and December 4-8, 2000
Analytical Dates: December 20, 2000 - January 23, 2001

SUBJECT SELECTION:

Thirty two (32) healthy male volunteers were enrolled for this study. The mean age and weight of these volunteers were 33 years and 74 kg, respectively . Five subjects' age was in the range of 19-40 years, the remaining were in the 41-45 years range. Subjects who entered this study were selected based on acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions, and appropriate subject selection criteria outlined in the study protocol.

STUDY DESIGN: The clinical study was conducted as a multiple-dose, randomized, two-treatment, two-period crossover evaluation with a washout period of 7 days between the two dosing days.

TREATMENTS: The lot numbers of the test (A) and reference (B) products tested in this study were identical to those used for the single dose fasting study. Single doses of each product were administered for five consecutive days between 8:00-9:00 A.M. using the randomization schedule given in table 13.

MEALS: Subject fasted overnight before the first dose in each period. Water was prohibited for 1 hour before and 1 hour after dosing. Standard meals were provided at 4 and 9 hours after each dose.

SAMPLE COLLECTION AND STORAGE:

Sample: Blood samples were collected under conditions to minimize exposure to light.
Sampling times: 0 (pre-dose) on day 1 and 3-5 before dosing and 1, 2, 3, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 15, 16, 17, 18, 20 and 24 hours after the last dose.
Sample Storage: Plasma was separated and stored at -20 ± 10 °C until analysis.

HEMODYNAMIC EVALUATIONS: Same as mentioned for the single dose fasting study.

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RESULTS:

Clinical Study Conduct:

Number of subjects dosed:	32
Number of subjects completing the study:	29 (Subject #6 was withdrawn due to an abnormal EKG during period 1. Subject #25 withdrew for personal reasons, and subject #32 was withdrawn due to low heart rate during period 1).
Adverse events:	A variety of clinical events were reported in a number of subjects (vol. 1.9). Many events were unrelated to drug treatments. Distribution of drug-related events was : TRT A - 13, TRT B-25.
Protocol deviations:	Minor deviation related to blood draw times were reported for 31 samples. In the reviewer's opinion these deviations should not affect bioavailability comparison.

PK Data:

Individual-subject plasma concentration data: Diltiazem and desmethyl-diltiazem plasma concentration data are given in appendix 2 (vol. 1.9). Line graphs depicting individual-subject concentration vs. time profiles are included in the same section.

Mean plasma concentration profiles: See tables 13 & 16 (attachment).

AUC and C_{max} data: See tables 14 &17 (attachment) for individual subject values, and Test/Reference ratios of AUC, and C_{max}.

Bioequivalence Evaluation: Bioequivalence evaluation is based on 29 subjects' data.

Mean parametric values and test/ref ratios: See tables 15 and 18 (attachment).

90% confidence intervals: The 90% confidence intervals for AUC and C_{max} were within the acceptable limit of 80-125% (tables 15 & 18, attachment).

Sequence Effect: Not detected based on reviewer's analyses.

In Vitro Dissolution Testing

Method: Dissolution testing was performed using the USP apparatus II (paddle) operated at 100 rpm. The USP method (USP XXIV, Page 575, *Test 3 for once/daily products*) recommends 0.1 N HCl as the dissolution medium. The firm has tested the all strengths of the test and reference products in this medium. In addition the firm has compared the dissolution profiles of 300 mg capsules of the test and reference products in buffers of pH 1.1, 4.4 and 6.3.

Test and reference products: Lots of diltiazem hydrochloride 300-mg extended release capsules of the test and reference products used for dissolution testing and the bioequivalence studies were identical. Lot numbers for the 240-mg, 180-mg and 120-mg products are listed in the table given below.

Results: Dissolution testing is summarized below. Dissolution testing meets USP specifications listed in the table below. The dissolution testing is acceptable.

***In vitro* Dissolution Testing (USP Method)**

Drug Product: Diltiazem HCl capsules
Dose Strength: 300, 240, 180 and 120mg

ANDA # 76-151, the raw data are given in vol. 1.15

Firm: **TorPharm**

Submission Date: August 29, 2001
File # **76151N801.doc**

Conditions of Dissolution Testing:

USP Apparatus II Paddle, RPM: 100 rpm
Units Tested: 12
Media: Four media (see below)
Specifications (USP): 6hr· ——— 12 hr· ———
18 hr· ———; 24 hr. NLT ——%, 30 hr.: NLT ———
Reference Drug: Cardizem^{R} CD ER capsules

Results of Dissolution Testing:

0.1N HCl		
Product	**Potency**	**F_2**
TEST	300 vs. 240 mg	81.30
	300 vs. 180 mg	94.90
	300 vs. 120 mg	89.63
REF	300 vs. 240 mg	86.40
	300 vs. 180 mg	63.63
	300 vs. 120 mg	59.23

TEST vs. REF		
Potency	**Medium**	**F2**
300 mg	0.1 N HCl	48.60
	Buffer pH 1.1	48.26
	Buffer pH 4.4	26.16
	Buffer pH 6.3	36.04

A. Media = 0.1N HCl

Sampling Time (Hr)	Test Product (T) Lot # FD-0118 Strength: **300mg** Mean (%)	Range (%)	%CV	Reference Product (R) Lot # 1009408 Strength: **300 mg** Mean (%)	Range (%)	%CV	**T/R**
2	18		16.0	1		31.0	**18.00**
4	23		14.0	8		12.0	**2.88**
6	26		13.0	34		5.0	**0.76**
12	41		7.0	40		5.0	**1.03**
18	62		4.0	56		4.0	**1.11**
24	79		2.0	93		1.0	**0.85**
30	87		2.0	98		1.0	**0.89**

Sampling Time (Hr)	Test Product (T) Lot # FD-0132 Strength: **240 mg** Mean (%)	Range (%)	%CV	Reference Product (R) Lot # 1021728 Strength: **240 mg** Mean (%)	Range (%)	%CV	**T/R**
6	26		8.0	35		5.0	**0.74**
12	39		5.0	39		5.0	**1.00**
18	59		4.0	58		58.0	**1.02**
24	76		3.0	95		1.0	**0.80**
30	86		2.0	99		1.0	**0.87**

Sampling Time (Hr)	Test Product (T) Lot # FD-0133 Strength: **180 mg** Mean (%)	Range (%)	%CV	Reference Product (R) Lot # 1023917 Strength: **180 mg** Mean (%)	Range (%)	%CV	**T/R**
6	27		13.0	34		7.0	**0.79**
12	42		8.0	38		8.0	**1.11**
18	62		5.0	47		8.0	**1.32**
24	78		78.0	88		4.0	**0.89**
30	87		3.0	91		5.0	**0.96**

Sampling Time (Hr)	Test Product (T) Lot # FD-0134 Strength: **120 mg** Mean (%)	Range (%)	%CV	Reference Product (R) Lot # 1018832 Strength: **120 mg** Mean (%)	Range (%)	%CV	**T/R**
6	25		18.0	31		7.0	**0.81**
12	40		8.0	34		8.0	**1.18**
18	61		3.0	45		8.0	**1.36**
24	77		3.0	92		2.0	**0.84**
30	86		3.0	98		2.0	**0.88**

B. Media = Buffer pH 1.1

Sampling Time (Hr)	Test Product (T) Lot # FD-0118 Strength: **300mg**			Reference Product (R) Lot # 1009408 Strength: **300 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
2	10		14.0	0		107.0	-
4	25		7.0	6		24.0	**4.17**
6	29		7.0	34		5.0	**0.85**
12	42		5.0	40		6.0	**1.05**
18	61		2.0	53		4.0	**1.15**
24	79		2.0	91		2.0	**0.87**
30	87		2.0	97		2.0	**0.90**

C. Media = Phosphate Buffer pH 4.4

Sampling Time (Hr)	Test Product (T) Lot # FD-0118 Strength: **300mg**			Reference Product (R) Lot # 1009408 Strength: **300 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
2	17		8.0	13		18.0	**1.31**
4	24		8.0	42		7.0	**0.57**
6	26		7.0	45		7.0	**0.58**
12	32		7.0	78		6.0	**0.41**
18	40		6.0	53		4.0	**0.75**
24	61		4.0	110		1.0	**0.55**
30	-		-	-		-	-

C. Media = Phosphate Buffer pH 6.3

Sampling Time (Hr)	Test Product (T) Lot # FD-0118 Strength: **300mg**			Reference Product (R) Lot # 1009408 Strength: **300 mg**			**T/R**
	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV	
2	31		7.0	1		36.0	**31.00**
4	38		20.0	29		9.0	**1.31**
6	51		3.0	41		4.0	**1.24**
12	74		3.0	55		4.0	**1.35**
18	81		3.0	100		1.0	**0.81**
22	91		1.0	102		1.0	**0.89**

Waiver Request: The firm has submitted a request for waiver of *in vivo* bioequivalence study requirements for its diltiazem hydrochloride and 240 mg, 180 mg and 120 mg extended release capsules based on:

A. Acceptable bioequivalence studies on diltiazem hydrochloride 300-mg extended release capsules.

B. Compositional proportionality of diltiazem hydrochloride and 240-mg, 180-mg and 120-mg extended release capsules to diltiazem hydrochloride 300 mg extended release capsule (see below).

C. Acceptable dissolution data for diltiazem hydrochloride 300-mg, and 240-mg, 180-mg and 120-mg extended release capsules.

Test Products' Compositions (Not to be released under FOI):

Ingredient	mg/Capsule			
	120-mg	180-mg	240-mg	300-mg
Diltiazem HCl, USP	120	180	240	300
Dibutyl Phthalate*	[redacted]			
Eudagrit [redacted] Methacrylic Acid Co-polymer Dispersion, NF				
Methlyclellulose, [redacted] USP				
Microcrystaline Cellulose [redacted], US'				
Polysorbate [redacted] NF				
Talc [redacted] USP				
Triethyl Citrate, NF				
[redacted] P				
Total	*175.6*	*264.1*	*352.1*	*440.1*

[redacted]

The test product is formulated as a mixture of three types of [redacted] The ratio [redacted] Type 1:Type 2: type 3) of in the test products are 1:1:3. The three [redacted] types have different release rates.

Comments

1. This firm conducted a fasting bioequivalence study on its diltiazem hydrochloride 300 mg extended release capsule and the reference product, Cardizem CD® 300 mg extended release capsule. The results of this study demonstrate that under fasting conditions, TorPharm's diltiazem hydrochloride 300 mg extended release capsule is bioequivalent to the reference product, Cardizem CD® 300 mg extended release capsule.

2. The sponsor also compared the bioavailability of the test and reference products after ingestion of a high fat meal. The results of this study demonstrate comparable bioavailability of the test and reference products under non-fasting conditions.

3. The firm also determined bioequivalence of the test and reference products at steady state in a multiple dose study.

3. The *in vitro* dissolution conducted by the firm on diltiazem hydrochloride 300-mg and 240 mg, 180 mg and 120 mg extended release capsules meets the USP specifications.

4. Compositions of the 240 mg, 180 mg and 120 mg extended release capsules of the test product are proportionally similar to that of its 300 mg extended release capsule. Based on satisfactory dissolution and composition proportionality between the 300 mg and 240 mg, 180 mg and 120 mg extended release capsules, the waiver of *in vivo* bioequivalence study requirements for diltiazem hydrochloride 240 mg, 180 mg and 120 mg extended release capsules may be granted.

Recommendations

1. The *in-vivo* bioequivalence study (single-dose)conducted under fasting condition by TorPharm on its diltiazem hydrochloride 300-mg extended release capsule, lot #FDA0118A, comparing it to the reference product Cardizem CD® 300-mg extended release capsule, lot #1009408, manufactured by Aventis, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, TorPharm's diltiazem hydrochloride 300-mg extended release capsules are bioequivalent to Cardizem CD® 300-mg extended release capsules, manufactured by Aventis .

2. The *in-vivo* study (single-dose) conducted under non- fasting condition by TorPharm comparing bioavailability of its diltiazem hydrochloride 300-mg extended release capsule, lot #FDA0118A, to that of the reference product Cardizem CD® 300-mg extended release capsule, lot #1009408, manufactured by Aventis, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, bioavailability of TorPharm's diltiazem hydrochloride 300-mg

extended release capsules is similar to that of Cardizem CD® 300-mg extended release capsules, manufactured by Aventis.

3. The *in-vivo* steady-state study (multiple-dose) conducted under fasting condition by TorPharm on its diltiazem hydrochloride 300-mg extended release capsule, lot #FDA0118A, and the reference product Cardizem CD® 300-mg extended release capsule, lot #1009408, manufactured by Aventis, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates the steady-state bioequivalence of TorPharm's diltiazem hydrochloride 300-mg extended release capsules and the Cardizem CD® 300-mg extended release capsules, manufactured by Aventis .

4. The *in vitro* dissolution testing conducted by TorPharm on its diltiazem hydrochloride 300-mg and 240-mg, 180-mg and 120-mg, lot # FD-0118A, FD0132, FD0133 and FD-0134, respectively, is acceptable. The firm has conducted acceptable *in vivo* bioequivalence studies comparing the 300-mg extended release capsule of the test product with the 300-mg extended release capsule of the reference product, Cardizem CD®, manufactured by Aventis. The formulations of diltiazem hydrochloride 240-mg, 180-mg and 120-mg extended release capsule are proportionally similar to the 300-mg extended release capsule of the test product, which underwent *in vivo* bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 240-mg, 180-mg and 120-mg extended release capsule of the test product may be granted. The 240-mg, 180-mg and 120-mg extended release capsules of the test product are therefore deemed bioequivalent to the 240-mg, 180-mg and 120-mg extended release capsule of the reference product, Cardizem CD®, Aventis .

5. The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of 0.1N HCl using USP XXIV apparatus II (paddle) at 100 rpm. The dissolution testing should meet the following USP specifications.

Time (hours)	% Dissolution
6	[redacted]
12	[redacted]
18	[redacted]
24	Not less than [redacted]
30	Not less than [redacted]

From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence on its diltiazem hydrochloride 300 mg and 240 mg, 180 mg and 120 mg extended release capsule.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence.

6/18/2002

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

CONCUR: _____ DATE: 7/3/2002

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence.

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APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 76-151 APPLICANT: TorPharm

DRUG PRODUCTS: Diltiazem hydrochloride USP, 300-mg, 240-mg, 180-mg and 120-mg extended release capsules.

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in the Test 3 of USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA: 76-151
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer CDOS 6-14-02
HFD-655/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner for 7/3/2002

6/18/02

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BIOEQUIVALENCY - ACCEPTABLE **Submission date: August 29, 20001**

1. **FASTING STUDY** (STF) Strength: 300 mg
Clinical: **Outcome: AC**
Analytical

2. **NON-FASTING STUDY** (STF) Strength: 300 mg
Clinical: **Outcome: AC**
Analytical:

3. **STEADY-STATE ASTING STUDY** (STS) Strength: 300 mg
Clinical: **Outcome: AC**
Analytical

DISSOLUTION DATA (DIS) Strength: 300 mg
Outcome: AC

4. **DISSOLUTION /WAIVER** (WAI) Strengths: 240 mg
Outcome: AC

5. **DISSOLUTION /WAIVER** (WAI) Strengths: 180 mg
Outcome: AC

6. **DISSOLUTION /WAIVER** (WAI) Strengths: 120 mg
Outcome: AC

WinBio Comments: The single dose fasting and non-fasting and multiple-dose bioequivalence studies are acceptable. Dissolution testing is acceptable. The waiver request for 240-mg, 180-mg and 120-mg extended release capsules may be granted.

Table 1: Mean Plasma Cocentration profiles of diltiazem (Single-dose fasting study, ANDA 76-151, N=29)

Time	TEST (A)		REF (B)		A/B
(Hr.)	Mean	%CV	Mean	%CV	
0	0.00	_	0.00	-	-
2	64.34	57.67	1.41	78.31	45.69
3	107.43	45.91	1.83	91.24	58.74
4	124.51	34.19	25.74	114.84	4.84
5	128.54	33.17	128.56	43.48	1.00
6	112.73	32.79	140.21	39.91	0.80
7	102.47	34.72	114.45	36.98	0.90
8	95.50	37.57	96.72	39.93	0.99
10	100.86	44.63	77.91	49.31	1.29
12	109.91	46.30	94.59	47.30	1.16
14	114.49	38.76	118.88	43.40	0.96
16	111.54	38.31	129.30	40.84	0.86
18	92.60	38.59	113.74	37.27	0.81
20	74.82	36.52	95.27	37.49	0.79
24	61.83	40.83	76.61	35.93	0.81
28	52.00	48.42	63.05	46.19	0.82
32	34.35	56.46	40.71	52.10	0.84
36	22.42	67.68	28.04	60.14	0.80
48	6.69	90.12	8.18	82.85	0.82
60	2.03	111.79	2.62	106.25	0.77

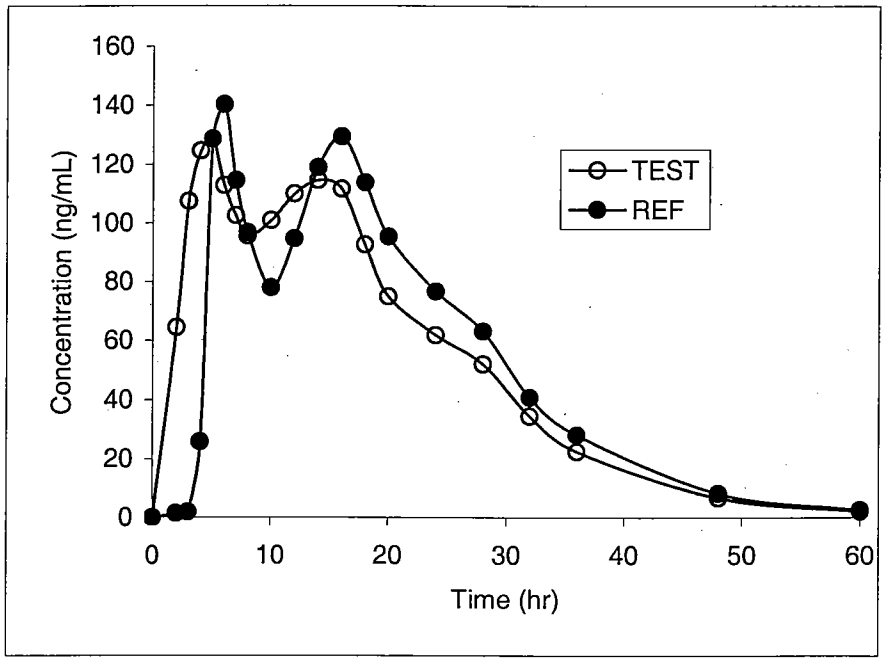

Table 2: Diltiazem Parametric data (Single-dose fasting study, ANDA 76-151, N=29)

										TEST/REF		
SUB	SEQ	TRT	AUCT	AUCINF	RATIO	CMAX	TMAX	KEL	T1/2	AUCT	AUCI	CMAX
1	BA	A										
2	AB	A										
3	AB	A										
4	BA	A										
5	AB	A										
6	BA	A										
7	AB	A										
8	AB	A										
9	BA	A										
10	BA	A										
11	AB	A										
12	BA	A										
14	AB	A										
15	AB	A										
16	AB	A										
17	BA	A										
18	BA	A										
19	AB	A										
20	AB	A										
21	BA	A										
22	AB	A										
23	BA	A										
25	BA	A										
26	AB	A										
27	BA	A										
29	BA	A										
30	AB	A										
31	BA	A										
32	BA	A										
		Mean	2963.07	2985.34	0.99	145.49	6.34	0.12	6.24			
		%CV	38.13	38.59	0.99	36.18	67.17	19.26	21.07			
1	BA	B										
2	AB	B										
3	AB	B										
4	BA	B										
5	AB	B										
6	BA	B										
7	AB	B										
8	AB	B										
9	BA	B										
10	BA	B										
11	AB	B										
12	BA	B										
14	AB	B										

15	AB	B							
16	AB	B							
17	BA	B							
18	BA	B							
19	AB	B							
20	AB	B							
21	BA	B							
22	AB	B							
23	BA	B							
25	BA	B							
26	AB	B							
27	BA	B							
29	BA	B							
30	AB	B							
31	BA	B							
32	BA	B							
		Mean	2971.62	3000.62	0.99	155.13	8.03	0.11	6.50
		%CV	40.49	40.99	0.99	38.76	57.18	22.96	26.24

Table 3: Diltiazem Parametric Data (ANDA 76151, Fasting Study, N=29)

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC	2963.07	38.13	2971.62	40.49	**1.00**	**95.65-106.71**	14.41%
(ng/mL*hr)	*2953.46*		*2969.18*		***0.99***		
AUCI	2985.34	38.59	3000.62	40.99	***0.99***	**94.46-106.32**	14.44%
ng/mL*hr)	*2975.75*		*2998.24*		***0.99***		
CMAX	145.49	36.18	155.13	38.76	***0.94***	**87.87-102.81**	16.30%
(ng/mL)	*43.32*		*42.06*		***1.03***		
TMAX (hr)	6.34	67.17	8.03	57.18	***0.79***		
KEL (hr-1)	0.12	19.26	0.11	22.96	***1.02***		
THALF (hr)	6.24	21.07	6.50	26.24	***0.96***		

Data given in italics are based on LS means
ISV = Intrasubject Variability
90% CI are based on the the reviewer's calculations using the log-tranformed data

Table 4: Mean Plasma Concentration profiles of Desmethyl-diltiazem (Single-dose fasting study, ANDA 76-151, N=29)

Time	TEST (A)		REF (B)		A/B
(Hr.)	Mean	%CV	Mean	%CV	
0	0.00	-	0.00	-	-
2	15.27	44.96	0.45	49.96	33.56
3	26.71	35.95	0.68	50.52	39.45
4	33.09	25.88	5.71	100.88	5.79
5	37.24	18.73	23.98	40.21	1.55
6	37.03	20.75	30.80	27.12	1.20
7	36.34	22.14	31.87	24.61	1.14
8	35.59	23.91	30.87	25.58	1.15
10	36.22	28.38	28.68	28.68	1.26
12	37.98	31.49	31.28	28.73	1.21
14	40.00	29.81	36.68	25.82	1.09
16	40.08	26.84	41.56	25.42	0.96
18	36.31	27.44	39.81	23.58	0.91
20	31.81	28.08	35.60	23.45	0.89
24	27.42	25.92	30.46	23.35	0.90
28	24.82	32.18	28.06	26.33	0.88
32	18.76	34.63	21.14	27.24	0.89
36	14.24	43.32	16.61	34.26	0.86
48	5.43	58.59	6.23	45.47	0.87
60	2.21	78.83	2.56	61.67	0.86

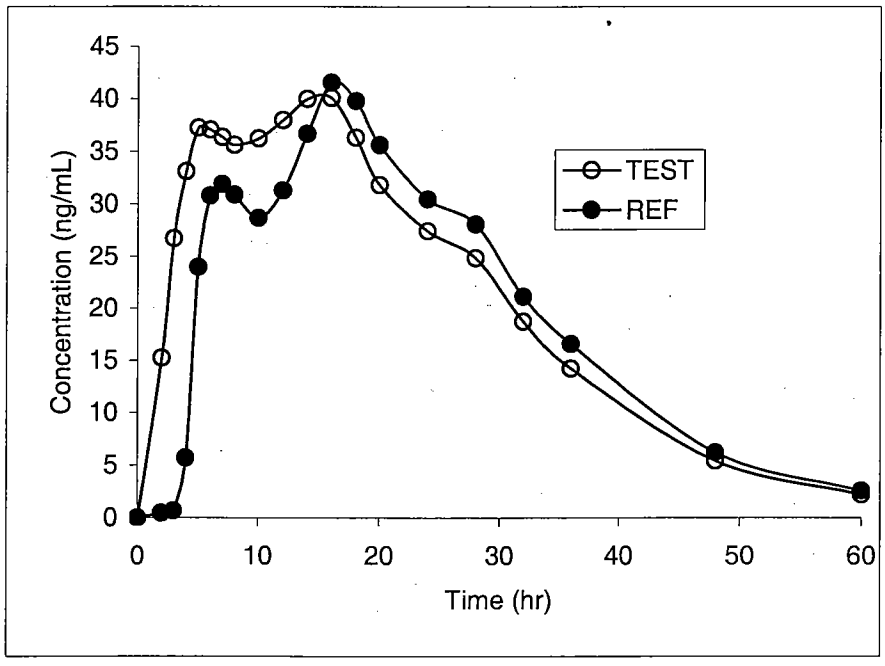

Table 5: Desmethyl-Diltiazem Parametric data (Single-dose fasting study, ANDA 76-151, N=29)

										TEST/REF		
SUB	SEQ	TRT	AUCT	AUCINF	RATIO	CMAX	TMAX	KEL	T1/2	AUCT	AUCI	CMAX
1	BA	A										
2	AB	A										
3	AB	A										
4	BA	A										
5	AB	A										
6	BA	A										
7	AB	A										
8	AB	A										
9	BA	A										
10	BA	A										
11	AB	A										
12	BA	A										
14	AB	A										
15	AB	A										
16	AB	A										
17	BA	A										
18	BA	A										
19	AB	A										
20	AB	A										
21	BA	A										
22	AB	A										
23	BA	A										
25	BA	A										
26	AB	A										
27	BA	A										
29	BA	A										
30	AB	A										
31	BA	A										
32	BA	A										
		Mean	**1199.76**	**1230.86**	**0.97**	**43.41**	**11.52**	**0.08**	**8.48**			
		%CV	**26.26**	**27.33**	**0.96**	**27.44**	**41.29**	**18.94**	**21.68**			
1	BA	B										
2	AB	B										
3	AB	B										
4	BA	B										
5	AB	B										
6	BA	B										
7	AB	B										
8	AB	B										
9	BA	B										
10	BA	B										
11	AB	B										
12	BA	B										

14	AB	B							
15	AB	B							
16	AB	B							
17	BA	B							
18	BA	B							
19	AB	B							
20	AB	B							
21	BA	B							
22	AB	B							
23	BA	B							
25	BA	B							
26	AB	B							
27	BA	B							
29	BA	B							
30	AB	B							
31	BA	B							
32	BA	B							
		Mean	**1143.48**	**1178.55**	**0.97**	**42.67**	**15.34**	**0.08**	**8.61**
		%CV	**23.33**	**23.93**	**0.98**	**24.34**	**17.44**	**17.82**	**19.31**

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Table 6: Desmethyl Diltiazem Parametric Data (ANDA 76151, Fasting Study, N=29)

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC	1199.76	26.26	1143.48	23.33	**1.05**	**101.39-107.51**	8.02%
(ng/mL*hr)	*1198.04*		*1142.67*		***1.05***		
AUCI	1230.86	27.33	1178.55	23.93	***1.04***	**100.82-106.93**	8.14%
ng/mL*hr)	*1229.05*		*1177.75*		***1.04***		
CMAX	43.41	27.44	42.67	24.34	***1.02***	**97.42-105.57**	11.09%
(ng/mL)	*43.32*		*42.06*		***1.03***		
TMAX (hr)	11.52	41.29	15.34	17.44	***0.75***		
KEL (hr-1)	0.08	18.94	0.08	17.82	***1.02***		
THALF (hr)	8.48	21.68	8.61	19.31	***0.98***		

Data given in italics are based on LS means
ISV = Intrasubject Variability
90% CI are based on the the reviewer's calculations using the log-tranformed data

Table 7: Plasma Concentration Profiles of Diltiazem (ANDA 76-151, Fed Study, N=17)

Time	TRT-A		TRT-B		TRTC	
(Hr)	Mean	%CV	Mean	%CV	Mean	%CV
0	0.00	-	0.00	-	0.00	-
2	18.38	85.11	0.97	123.10	62.00	35.70
3	62.57	58.25	1.79	84.51	109.95	38.28
4	86.57	65.67	2.44	82.45	127.64	34.97
5	97.71	56.35	23.01	111.95	127.44	32.54
6	111.19	46.16	67.14	63.32	117.14	30.15
7	114.47	40.25	95.75	46.68	107.66	31.76
8	113.98	48.73	104.16	43.04	104.64	35.76
10	97.83	42.25	82.80	40.63	111.73	45.13
12	116.78	41.42	77.91	44.90	114.63	44.06
14	128.76	33.02	96.31	44.80	113.58	38.40
16	125.94	30.28	102.56	37.80	106.14	34.69
18	118.11	33.31	105.48	36.18	93.05	32.38
20	102.64	31.47	100.62	35.54	83.45	35.50
24	87.81	38.35	93.42	34.80	69.59	39.99
28	67.74	39.83	74.44	38.53	54.59	41.59
32	38.67	46.90	45.36	46.69	32.32	47.98
36	24.88	51.16	30.17	50.42	21.87	48.54
42	13.96	53.18	16.33	51.21	11.75	48.78
48	7.98	55.47	9.66	49.82	6.93	50.14
54	3.98	65.05	4.89	59.57	3.72	60.11

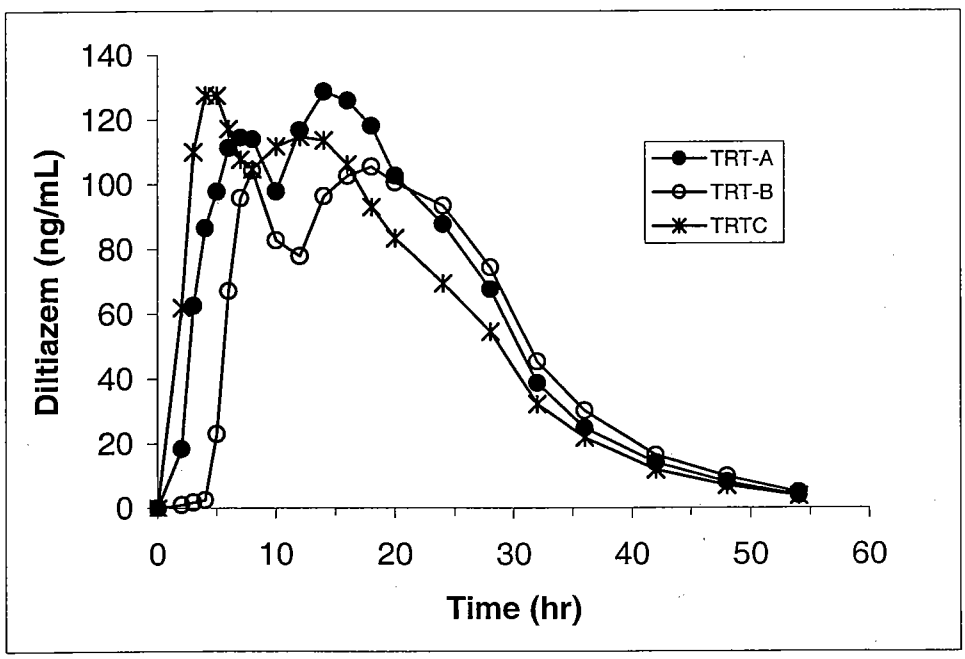

Table 8: Diltiazem Individual Parameters (ANDA 76-151, FED Study, N=17)

		TEST-FED (A)							REF-FED (B)						
SUB	SEQ	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF
2	ABC														
3	CBA														
4	BAC														
5	CAB														
6	ACB														
7	CBA														
8	CAB														
9	BCA														
10	ACB														
11	ABC														
12	BAC														
13	BCA														
14	BAC														
15	ABC														
16	CBA														
17	CAB														
18	ACB														
	Mean	**3215.73**	**3256.39**	**0.99**	**147.21**	**12.83**	**0.10**	**6.75**	**2753.93**	**2804.01**	**0.98**	**124.75**	**13.65**	**0.10**	**6.92**
	%CV	**35.55**	**35.79**	**0.61**	**38.04**	**39.39**	**12.12**	**12.32**	**35.27**	**35.47**	**0.83**	**34.96**	**40.28**	**12.22**	**11.89**
	GeoMean	***3001.52***	***3036.75***	***0.99***	***137.08***	***11.51***	***0.10***	***6.71***	***2595.77***	***2640.77***	***0.98***	***117.83***	***12.49***	***0.10***	***6.87***

		TEST-FAST (C)							A/B			A/C		
SUB	SEQ	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF	AUC	AUCI	Cmax	AUC	AUCI	Cmax
2	ABC													
3	CBA													
4	BAC													
5	CAB													
6	ACB													
7	CBA													
8	CAB													
9	BCA													
10	ACB													
11	ABC													
12	BAC													
13	BCA													
14	BAC													
15	ABC													
16	CBA													
17	CAB													
18	ACB													
	Mean	**3070.30**	**3109.93**	**0.99**	**147.16**	**7.66**	**0.10**	**7.06**	**1.17**	**1.16**	**1.21**	**1.19**	**1.19**	**1.11**
	%CV	**32.31**	**32.40**	**0.74**	**31.92**	**55.96**	**16.22**	**16.21**	**16.44**	**16.52**	**30.56**	**54.80**	**54.91**	**50.96**
	GeoMean	***2899.98***	***2936.87***	***0.99***	***139.71***	***6.61***	***0.10***	***6.97***	***1.16***	***1.15***	***1.16***	***1.04***	***1.03***	***0.98***

Table 9: Parametric Data for Diltiazem (ANDA 76-151, Non-fasting Study, N=17)

Parameter	TRT-A		TRT-B		TRT-C		A/B	A/C
	Mean	%CV	Mean	%CV	Mean	%CV		
AUC	3215.73	35.55	2753.93	35.27	3070.30	32.31	1.17	1.05
(ng/ml*hr)	***3001.52***		***2595.77***		***2899.98***		***1.16***	***1.04***
AUCI	3256.39	35.79	2804.01	35.47	3109.93	32.40	1.16	1.05
(ng/ml*hr)	***3036.75***		***2640.77***		***2936.87***		***1.15***	***1.03***
CMAX (ng/mL)	147.21	38.04	124.75	34.96	147.16	31.92	1.18	1.00
	137.08		***117.83***		***38.93***		***1.16***	***3.52***
TMAX (Hr)	12.83	39.39	13.65	40.28	7.66	55.96	0.94	1.67
KEL	0.10	12.12	0.10	12.22	0.10	16.22	1.02	1.03
THALF (Hr)	6.75	12.32	6.92	11.89	7.06	16.21	0.98	0.96

Data given in itaics are based on geometeric means

Table 10: Plasma Concentration Profiles of Desmethyl-diltiazem (ANDA 76-151, Fed Study, N=17)

Time	TRT-A		TRT-B		TRTC	
(Hr)	Mean	%CV	Mean	%CV	Mean	%CV
0	0.00	#VALUE!	0.00	#VALUE!	0.00	#VALUE!
2	3.63	77.57	0.21	81.54	13.22	26.84
3	12.26	37.59	0.46	66.46	23.61	28.55
4	18.82	38.06	0.81	97.18	29.18	22.66
5	25.58	31.32	6.12	136.62	33.95	20.71
6	29.88	26.27	15.69	62.89	33.59	18.96
7	32.48	23.48	23.76	36.32	33.34	20.29
8	34.24	19.16	27.74	23.67	34.20	23.68
10	32.88	24.31	28.82	22.23	35.35	30.43
12	35.68	23.92	28.67	25.70	36.74	31.59
14	37.88	23.45	31.16	28.77	36.67	27.82
16	38.61	20.32	33.10	28.11	36.51	26.28
18	36.99	20.84	33.84	25.80	34.19	23.81
20	34.94	18.80	32.87	21.90	32.12	24.64
24	31.37	28.42	31.49	25.32	27.95	26.38
28	27.98	31.12	30.11	27.99	25.06	30.46
32	21.28	34.94	22.96	36.10	18.75	39.97
36	15.80	40.49	17.59	38.38	14.54	40.26
42	9.85	44.37	11.20	41.19	9.00	44.66
48	6.88	46.22	7.71	43.26	6.02	43.86
54	4.37	54.65	4.97	48.47	4.03	55.49

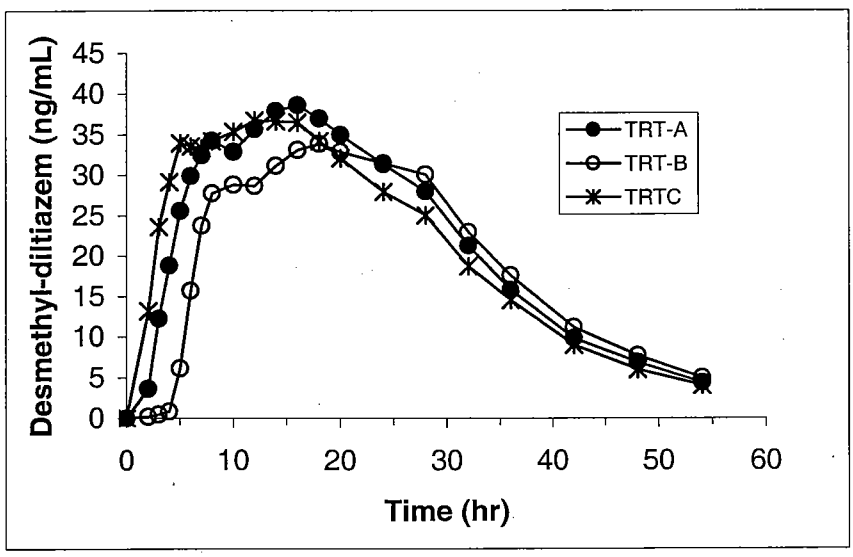

Table 11: Desmethyl-diltiazem Individual Parameters (ANDA 76-151, FED Study, N=17)

		TEST-FED (A)							REF-FED (B)						
SUB	SEQ	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF
2	ABC														
3	CBA														
4	BAC														
5	CAB														
6	ACB														
7	CBA														
8	CAB														
9	BCA														
10	ACB														
11	ABC														
12	BAC														
13	BCA														
14	BAC														
15	ABC														
16	CBA														
17	CAB														
18	ACB														
	Mean	**1160.95**	**1224.19**	**0.95**	**40.39**	**14.30**	**0.07**	**9.48**	**1053.18**	**1127.11**	**0.94**	**36.73**	**17.53**	**0.07**	**9.82**
	%CV	**24.25**	**25.86**	**2.24**	**19.27**	**25.66**	**14.33**	**13.55**	**25.54**	**26.79**	**2.75**	**23.64**	**31.13**	**15.50**	**14.01**
	GeoMean	***1129.92***	***1187.27***	***0.95***	***39.67***	***13.76***	***0.07***	***9.39***	***1023.39***	***1091.68***	***0.94***	***35.81***	***16.49***	***0.07***	***9.72***

		TEST-FAST (C)							A/B			A/C		
SUB	SEQ	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF	AUC	AUCI	Cmax	AUC	AUCI	Cmax
2	ABC													
3	CBA													
4	BAC													
5	CAB													
6	ACB													
7	CBA													
8	CAB													
9	BCA													
10	ACB													
11	ABC													
12	BAC													
13	BCA													
14	BAC													
15	ABC													
16	CBA													

17	CAB														
18	ACB														
	Mean	1141.45	1200.78	0.95	40.06	12.07	0.07	9.66	##	1.11	1.09	1.12	1.02	1.03	1.03
	%CV	25.73	27.00	2.29	24.54	31.89	16.23	15.63	##	8.04	8.39	15.16	8.02	7.86	12.76
	GeoMean	*1106.39*	*1161.03*	*0.95*	*38.93*	*11.32*	*0.07*	*9.55*	*#*	*1.10*	*1.09*	*1.11*	*1.02*	*1.02*	*1.02*

Table 12: Parametric Data for Desmethyl-diltiazem (ANDA 76-151, Non-fasting Study, N=17)

Parameter	TRT-A		TRT-B		TRT-C		A/B	A/C
	Mean	%CV	Mean	%CV	Mean	%CV		
AUC (ng/ml*hr)	1160.95	24.25	1053.18	25.54	1141.45	25.73	1.10	1.02
	1129.92		***1023.39***		***1106.39***		***1.10***	***1.02***
AUCI (ng/ml*hr)	1224.19	25.86	1127.11	26.79	1200.78	27.00	1.09	1.02
	1187.27		***1091.68***		***1161.03***		***1.09***	***1.02***
CMAX (ng/mL)	40.39	19.27	36.73	23.64	40.06	24.54	1.10	1.01
	39.67		***35.81***		***38.93***		***1.11***	***1.02***
TMAX (Hr)	14.30	25.66	17.53	31.13	12.07	31.89	0.82	1.18
KEL	0.07	14.33	0.07	15.50	0.07	16.23	1.03	1.01
THALF (Hr)	9.48	13.55	9.82	14.01	9.66	15.63	0.97	0.98

Data given in itaics are based on geometeric means

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ON ORIGINAL

Table 13: Mean Plasma Concentration profiles of diltiazem (Multple dose study, ANDA 76-151, N=29)

Time	TEST (A)		REF (B)		A/B
(Hr.)	Mean	%CV	Mean	%CV	
-96	0.00	-	0.00	-	-
-48	84.96	52.42	113.14	56.79	0.75
-24	88.90	52.53	119.15	54.88	0.75
0	89.36	54.78	119.00	58.11	0.75
2	182.06	46.87	107.57	60.01	1.69
3	238.03	38.71	97.51	59.69	2.44
4	245.17	38.38	129.43	66.23	1.89
5	241.79	36.60	246.66	52.58	0.98
6	219.90	38.61	249.38	46.79	0.88
7	202.34	41.64	224.69	47.45	0.90
8	187.57	38.56	204.73	49.54	0.92
9	174.71	44.50	183.78	55.66	0.95
10	174.46	43.97	175.64	54.90	0.99
12	166.48	48.95	173.88	50.06	0.96
13	158.32	46.50	173.53	45.82	0.91
14	152.86	45.83	179.23	46.20	0.85
15	141.99	50.02	169.60	43.96	0.84
16	134.97	53.11	163.84	43.45	0.82
17	123.31	53.32	157.42	47.04	0.78
18	111.12	49.21	145.41	45.04	0.76
20	95.25	53.74	125.09	49.64	0.76
22	83.16	52.23	112.23	54.11	0.74
24	76.90	50.98	103.58	56.99	0.74

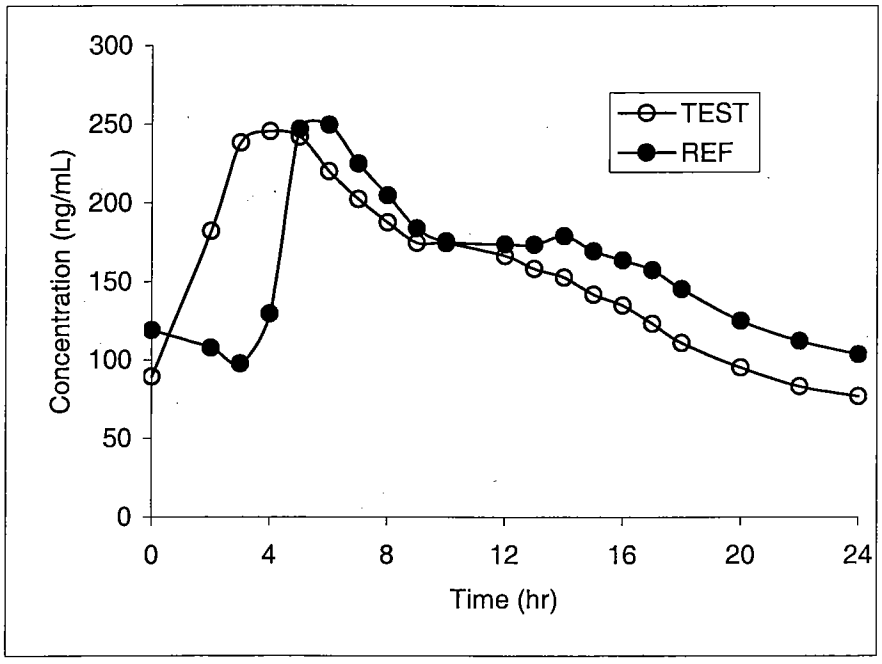

Table 14: Diltiazem Parametric data (Mutiple dose study, ANDA 76-151, N=29)

								TEST/REF				
SUB	SEQ	TRT	AUCT	CMAX	CMIN	TMAX	FLUC. 1	FLUC. 2	AUCT	CMAX	CMIN	FLUC. 1	FLUC. 2
1	AB	A											
2	BA	A											
3	BA	A											
4	BA	A											
5	AB	A											
7	AB	A											
8	AB	A											
9	BA	A											
10	BA	A											
11	AB	A											
12	AB	A											
13	AB	A											
14	BA	A											
15	BA	A											
16	BA	A											
17	AB	A											
18	AB	A											
19	BA	A											
20	BA	A											
21	AB	A											
22	AB	A											
23	BA	A											
24	BA	A											
26	BA	A											
27	AB	A											
28	BA	A											
29	AB	A											
30	BA	A											
31	AB	A											
		Mean	**3696.24**	**259.34**	**76.90**	**4.38**	**123.48**	**269.91**					
		%CV	**42.97**	**34.56**	**50.98**	**33.66**	**20.84**	**41.78**					
1	AB	B											
2	BA	B											
3	BA	B											
4	BA	B											
5	AB	B											
7	AB	B											
8	AB	B											
9	BA	B											
10	BA	B											
11	AB	B											
12	AB	B											
13	AB	B											

14 BA	B						
15 BA	B						
16 BA	B						
17 AB	B						
18 AB	B						
19 BA	B						
20 BA	B						
21 AB	B						
22 AB	B						
23 BA	B						
24 BA	B						
26 BA	B						
27 AB	B						
28 BA	B						
29 AB	B						
30 BA	B						
31 AB	B						
	Mean	3780.41	264.83	103.58	6.11	106.12	179.69
	%CV	48.19	47.39	56.99	25.62	29.99	47.44

Table 15: Diltiazem Parametric Data (ANDA 76151, Mutiple dose study, N=29)

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC (ng/mL*hr)	3696.24	42.97	3780.41	48.19	**0.98**	**94.77-104.29**	16.01%
	3705.91		*3780.33*		***0.98***		
CMAX ng/mL*hr)	259.34	34.56	264.83	47.39	***0.98***	**95.26-106.48**	17.93%
	259.58		*264.86*		***0.98***		
CMIN (ng/mL)	76.90	50.98	103.58	56.99	***0.74***		
TMAX (hr)	4.38	33.66	6.11	25.62	***0.72***		
FLUC. 1[a]	123.48	20.84	106.12	29.99	***1.16***		
FLUC. 2[b]	269.91	41.78	179.69	47.44	***1.50***		

Data given in italics are based on LS means
ISV = Intrasubject Variability
90% CI are based on the the reviewer's calculations using the log-tranformed data

a = ((Cmax-Cmin)/Cavg)*100
b = ((Cmax-Cmin)/Cmin)*100

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ON ORIGINAL

Table 16: Mean Plasma Concentration profiles of Desmethyl-diltiazem (Multple dose study, ANDA 76-151, N=29)

Time	TEST (A)		REF (B)		A/B
(Hr.)	Mean	%CV	Mean	%CV	
-96	0.00	-	0.01	395.61	-
-48	39.18	33.67	44.26	29.52	0.89
-24	39.63	32.93	46.58	30.90	0.85
0	40.32	33.14	46.77	31.14	0.86
2	53.37	28.45	43.34	33.56	1.23
3	64.25	24.19	41.11	35.25	1.56
4	68.43	22.52	45.25	35.14	1.51
5	71.93	21.39	58.53	29.97	1.23
6	73.47	21.31	65.83	26.17	1.12
7	72.06	23.46	66.63	27.25	1.08
8	70.84	24.29	66.68	26.59	1.06
9	68.16	23.26	63.83	26.57	1.07
10	66.81	24.69	62.60	25.85	1.07
12	64.89	26.91	63.36	24.31	1.02
13	63.41	25.20	62.53	23.60	1.01
14	63.16	26.98	66.82	24.38	0.95
15	60.65	25.84	64.16	23.72	0.95
16	59.76	33.09	63.00	24.08	0.95
17	55.64	31.52	59.38	21.52	0.94
18	52.46	30.95	58.79	24.81	0.89
20	45.75	32.94	52.32	27.68	0.87
22	41.57	33.47	48.35	29.00	0.86
24	39.36	33.57	44.94	27.77	0.88

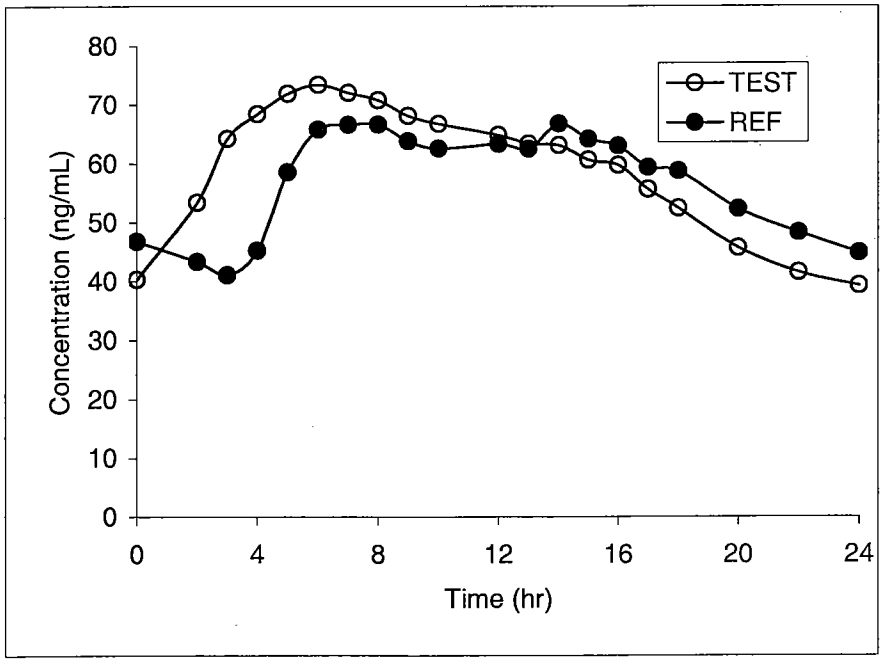

Table 17: Desmethyl-diltiazem Parametric data (Mutiple dose study, ANDA 76-151, N=29)

								TEST/REF				
SUB	SEQ	TRT	AUCT	CMAX	CMIN	TMAX	FLUC. 1	FLUC. 2	AUCT	CMAX	CMIN	FLUC. 1	FLUC. 2
1	AB	A											
2	BA	A											
3	BA	A											
4	BA	A											
5	AB	A											
7	AB	A											
8	AB	A											
9	BA	A											
10	BA	A											
11	AB	A											
12	AB	A											
13	AB	A											
14	BA	A											
15	BA	A											
16	BA	A											
17	AB	A											
18	AB	A											
19	BA	A											
20	BA	A											
21	AB	A											
22	AB	A											
23	BA	A											
24	BA	A											
26	BA	A											
27	AB	A											
28	BA	A											
29	AB	A											
30	BA	A											
31	AB	A											
		Mean	**1402.62**	**77.83**	**38.93**	**6.76**	**68.69**	**108.30**					
		%CV	**25.73**	**22.23**	**33.07**	**40.78**	**23.24**	**35.56**					
1	AB	B											
2	BA	B											
3	BA	B											
4	BA	B											
5	AB	B											
7	AB	B											
8	AB	B											
9	BA	B											
10	BA	B											
11	AB	B											
12	AB	B											

13 AB	B						
14 BA	B						
15 BA	B						
16 BA	B						
17 AB	B						
18 AB	B						
19 BA	B						
20 BA	B						
21 AB	B						
22 AB	B						
23 BA	B						
24 BA	B						
26 BA	B						
27 AB	B						
28 BA	B						
29 AB	B						
30 BA	B						
31 AB	B						
	Mean	**1360.34**	**72.77**	**39.25**	**10.04**	**59.95**	**90.52**
	%CV	**25.45**	**24.74**	**28.65**	**38.51**	**24.99**	**35.19**

Table 18: Desmethyl-diltiazem Parametric Data (ANDA 76151, Mutiple dose study, N=29)

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC (ng/mL*hr)	1402.62	25.73	1360.34	25.45	**1.03**	**100.89-105.31**	5.29%
	1405.72		*1362.86*		***1.03***		
CMAX ng/mL*[redacted])	77.83	22.23	72.77	24.74	***1.07***	**104.38-110.46**	6.68%
	77.96		*72.88*		***1.07***		
CMIN (ng/mL)	38.93	33.07	39.25	28.65	***0.99***		
TMAX (hr)	6.76	40.78	10.04	38.51	***0.67***		
FLUC. 1[a]	68.69	23.24	59.95	24.99	***1.15***		
FLUC. 2[b]	108.30	35.56	90.52	35.19	***1.20***		

Data given in italics are based on LS means
ISV = Intrasubject Variability
90% CI are based on the the reviewer's calculations using the log-tranformed data

a = ((Cmax-Cmin)/Cavg)*100
b = ((Cmax-Cmin)/Cmin)*100

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-151 APPLICANT: TorPharm Inc.

DRUG PRODUCT: Diltiazem Hydrochloride ER Capsules, USP
300 mg, 240 mg, 180 mg and 120 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Your proposed change of the dissolution specification at 30 hours from '*Not Less Than* ~' to 'Not Less Than —' is acceptable.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution should be conducted in 900 mL of 0.1N HCl using USP apparatus II (paddle) at 100 rpm. The dissolution testing should meet the following interim specifications.

Time (hours)	% Dissolution
6	[redacted]
12	[redacted]
18	[redacted]
24	Not less than [redacted]
30	Not less than [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 25 2002

Diltiazem Hydrochloride ER Capsules USP, 120, 180, 240 & 300 mg
ANDA #76-151
Reviewer: Lin-Whei Chuang
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TorPharm
Etobicoke, Ontario, Canada
Submission Date:
February 26, 2002

Review of a Minor Amendment

1. The original submission of 8/29/01 contained 3 BE studies on the 300 mg capsules, 4 dissolution data-sets on all 4 strengths, and waiver request for the 3 lower strengths. All 3 BE studies are acceptable, waivers are granted and the following USP dissolution method and specification (Test 3) are recommended (see review by G. Singh):

   The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of 0.1N HCl using USP XXIV apparatus II (paddle) at 100 rpm. The dissolution testing should meet the following USP specifications.

Time (hours)	% Dissolution
6	[redacted]
12	[redacted]
18	[redacted]
24	Not less than [redacted]
30	Not less than [redacted]

2. The current amendment is in response to a Chemistry Deficiency letter of 1/24/02. The Chemistry reviewer, A. Langowkski, E-mailed G. Singh of DBE on 6/20/02 stated that the applicant had some dissolution failures at **30 hours** for the stability batches and proposed a drug release specification of ***"NLT [redacted] at 30 hours"*** instead of the approved USP specification of ***"NLT [redacted] at 30 hours"***. The Chemistry reviewer is requesting comments from DBE on this change of drug release specification at 30 hours.

3. The firm compared the dissolution profiles of the stability batches to either product used in the BE studies, i.e., Cardizem CD 300 mg capsules or TorPharm's diltiazem 300 mg ER capsules which underwent in vivo BE studies. The F1 and F2 factors are summarized below:

Strength	Compared to Cardizem		Compared to TorPharm's 300 mg capsules	
	F1	F2	F1	F2
240 mg (lot #FD0132)	11.5-14	47.4-55.3	2-7.1	66-89.4
180 mg (lot #FD0133)	11.2-15.3	48.2-57.4	1.4-7.8	57.9-92.5
120 mg (lot #FD0134)	11.5-13.7	50-57	1-5.1	71.7-95.6

4. The stability data submitted by the firm indicated that failures at 30 hours are most likely due to the variation of dissolution method. For example, lot #FD0132A has 2 of 6 initially, 1 of 6 at 3 months, 2 of 6 at 6 months, none at 9 months, and 4 of 12 at 12 months that failed the 30-hour specification.

5. The firm states that at 30 hours, nearly all of an absorbed dose is eliminated since the mean $T_{1/2}$ is 6.3 hours.

6. The transit time through the GI tract is 24 hours, therefore any additional drug remaining in the dosage form will not likely be available for absorption in vivo.

7. Therefore, the difference between [redacted] release in vitro at 30 hours is not consequential in the plasma level profile.

8. TorPharm has submitted a request to the USP to revise the limit of in vitro drug release at 30 hours from "NLT [redacted]' to "NLT [redacted]' and will notify the Agency of the response from USP when it's received.

Reviewer's Comments (after consultation with N. Tran of DBE):

1. The firm's explanations are acceptable.

2. The Labeling Branch should be notified of the change of drug release specification at 30 hours from "NLT [redacted]' to "NLT [redacted].

Recommendation:

The new dissolution specification proposed by TorPharm for its Diltiazem Hydrochloride, USP, ER Capsules, 300 mg, 240 mg, 180 mg and 120 mg, is acceptable. The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of 0.1N HCl using

USP apparatus II (paddle) at 100 rpm. The dissolution testing should meet the following interim specifications.

Time (hours)	% Dissolution
6	[redacted]
12	[redacted]
18	[redacted]
24	Not less than [redacted]
30	Not less than [redacted]

Lin-Whei Chuang 8/12/02

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG

8/12/2002

Concur: [signature] Date: 10/25/2002

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

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APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #76-151
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Lin-Whei Chuang

Endorsements: (Final with Dates)
HFD-652/ L. Chuang LWC 8/12/02
HFD-652/ Y. Huang YH 8/12/2002
HFD-652/ K. Scardina
HFD-650/ D. Conner for RWL 10/25/2002

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BIOEQUIVALENCY - ACCEPTABLE submission date: 2/28/02

1. **STUDY AMENDMENT** (STA) Strength: 300, 240, 180, 120 mg
o/c **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

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ON ORIGINAL

Table 8: Diltiazem Individual Parameters (ANDA 76-151, FED Study, N=17)

		TEST-FED (A)							REF-FED (B)						
SUB	SEQ	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF
2	ABC														
3	CBA														
4	BAC														
5	CAB														
6	ACB														
7	CBA														
8	CAB														
9	BCA														
10	ACB														
11	ABC														
12	BAC														
13	BCA														
14	BAC														
15	ABC														
16	CBA														
17	CAB														
18	ACB														
	Mean	**3215.73**	**3256.39**	**0.99**	**147.21**	**12.83**	**0.10**	**6.75**	**2753.93**	**2804.01**	**0.98**	**124.75**	**13.65**	**0.10**	**6.92**
	%CV	**35.55**	**35.79**	**0.61**	**38.04**	**39.39**	**12.12**	**12.32**	**35.27**	**35.47**	**0.83**	**34.96**	**40.28**	**12.22**	**11.89**
	GeoMean	***3001.52***	***3036.75***	***0.99***	***137.08***	***11.51***	***0.10***	***6.71***	***2595.77***	***2640.77***	***0.98***	***117.83***	***12.49***	***0.10***	***6.87***

		TEST-FAST (C)							A/B			A/C		
SUB	SEQ	AUC	AUCI	Ratio	CMAX	TMAX	KEL	HALF	AUC	AUCI	Cmax	AUC	AUCI	Cmax
2	ABC													
3	CBA													
4	BAC													
5	CAB													
6	ACB													
7	CBA													
8	CAB													
9	BCA													
10	ACB													
11	ABC													
12	BAC													
13	BCA													
14	BAC													
15	ABC													
16	CBA													
17	CAB													
18	ACB													
	Mean	**3070.30**	**3109.93**	**0.99**	**147.16**	**7.66**	**0.10**	**7.06**	**1.17**	**1.16**	**1.21**	**1.19**	**1.19**	**1.11**
	%CV	**32.31**	**32.40**	**0.74**	**31.92**	**55.96**	**16.22**	**16.21**	**16.44**	**16.52**	**30.56**	**54.80**	**54.91**	**50.96**
	GeoMean	***2899.98***	***2936.87***	***0.99***	***139.71***	***6.61***	***0.10***	***6.97***	***1.16***	***1.15***	***1.16***	***1.04***	***1.03***	***0.98***

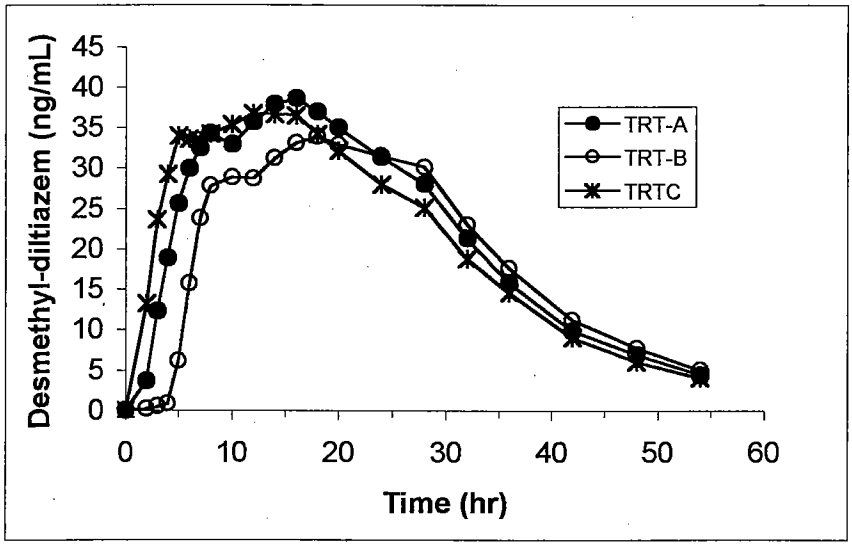
Table 9: Parametric Data for Diltiazem (ANDA 76-151, Non-fasting Study, N=17)

Parameter	TRT-A		TRT-B		TRT-C		A/B	A/C
	Mean	%CV	Mean	%CV	Mean	%CV		
AUC	3215.73	35.55	2753.93	35.27	3070.30	32.31	1.17	1.05
(ng/ml*hr)	***3001.52***		***2595.77***		***2899.98***		***1.16***	***1.04***
AUCI	3256.39	35.79	2804.01	35.47	3109.93	32.40	1.16	1.05
(ng/ml*hr)	***3036.75***		***2640.77***		***2936.87***		***1.15***	***1.03***
CMAX (ng/mL)	147.21	38.04	124.75	34.96	147.16	31.92	1.18	1.00
	137.08		***117.83***		***38.93***		***1.16***	***3.52***
TMAX (Hr)	12.83	39.39	13.65	40.28	7.66	55.96	0.94	1.67
KEL	0.10	12.12	0.10	12.22	0.10	16.22	1.02	1.03
THALF (Hr)	6.75	12.32	6.92	11.89	7.06	16.21	0.98	0.96

Data given in itaics are based on geometeric means

Table 10: Plasma Concentration Profiles of Desmethyl-diltiazem (ANDA 76-151, Fed Study, N=17)

Time	TRT-A		TRT-B		TRTC	
(Hr)	Mean	%CV	Mean	%CV	Mean	%CV
0	0.00	#VALUE!	0.00	#VALUE!	0.00	#VALUE!
2	3.63	77.57	0.21	81.54	13.22	26.84
3	12.26	37.59	0.46	66.46	23.61	28.55
4	18.82	38.06	0.81	97.18	29.18	22.66
5	25.58	31.32	6.12	136.62	33.95	20.71
6	29.88	26.27	15.69	62.89	33.59	18.96
7	32.48	23.48	23.76	36.32	33.34	20.29
8	34.24	19.16	27.74	23.67	34.20	23.68
10	32.88	24.31	28.82	22.23	35.35	30.43
12	35.68	23.92	28.67	25.70	36.74	31.59
14	37.88	23.45	31.16	28.77	36.67	27.82
16	38.61	20.32	33.10	28.11	36.51	26.28
18	36.99	20.84	33.84	25.80	34.19	23.81
20	34.94	18.80	32.87	21.90	32.12	24.64
24	31.37	28.42	31.49	25.32	27.95	26.38
28	27.98	31.12	30.11	27.99	25.06	30.46
32	21.28	34.94	22.96	36.10	18.75	39.97
36	15.80	40.49	17.59	38.38	14.54	40.26
42	9.85	44.37	11.20	41.19	9.00	44.66
48	6.88	46.22	7.71	43.26	6.02	43.86
54	4.37	54.65	4.97	48.47	4.03	55.49



FDA 0134A : 120mg

Initial	9 months	FD0133A 180mg 12 months	FD0132A 240mg 12 months	FD0118A 300mg 12 months
—	—	—	—	(—) ✓
—	—	—	—	—
—	—	—	—	(—)
—	—	(—)	—	—
—	—	—	—	—
—	—	—	—	—
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—	—	—	—	—
85.67	84.25	83.08	83.83	80.33

g: NLT — P F

109 mg

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-151 **SPONSOR: TorPharm**

DRUG AND DOSAGE FORM: Diltiazem HCl Extended-Release Capsules

STRENGTH (S): 300 mg, 240 mg, 180 mg and 120 mg

TYPES OF STUDIES: Single Dose Fasting and Non-fasting Studies and a Multiple Dose Study

CLINICAL STUDY SITE: [redacted]
AND SAMPLE ANAYSIS (S): [redacted]

STUDY SUMMARY: All three in vivo studies are acceptable.
DISSOLUTION: Acceptable
WAIVER: Waivers for the 240-mg, 180-mg and 120-mg capsules of the test product may be granted

DSI INSPECTION STATUS

Inspection needed: **No**	Inspection status: N/A	Inspection results: N/A
First Generic: ~~Yes~~ NO GSP New facility __No___ For cause __No___ Other _None__		

PRIMARY REVIEWER: (Gur J.P. Singh, Ph.D.) BRANCH: II

INITIAL: GJPSingh DATE: 5-21-02

TEAM LEADER: (Shriniwas Nerurkar, Ph.D.) BRANCH: II

INITIAL: SVNerurkar DATE: 6/18/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

for INITIAL: DPConner DATE: 7/3/2002

3.1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-151 SPONSOR : TorPharm Inc.

DRUG AND DOSAGE FORM : Diltiazem Hydrochloride ER Capsules, USP

STRENGTHS : 300 mg, 240 mg, 180 mg and 120 mg

TYPES OF STUDY : *In Vitro* Testing Specification Change

SUMMARY : : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Lin-Whei Chuang BRANCH : I

INITIAL : LWC DATE : 8/12/02 LWC

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : YCH DATE : 8/12/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for

INITIAL : Dale Conner DATE : 10/25/2002

Tor Pharm Inc.

ORIG AMENDMENT

N/Bio

COVER LETTER

BIOEQUIVALENCY AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 76-151 Diltiazem CD Capsules (Diltiazem Hydrochloride Extended-Release Capsules USP) 120 mg, 180 mg, 240 mg and 300 mg. The amendment is being submitted in response to the FDA Bioequivalency Comments letter dated December 18, 2002.

APPEARS THIS WAY
ON ORIGINAL

Samantha Law
Samantha Law
Supervisor, Regulatory Affairs

December 19, 2002
Date

RECEIVED
DEC 23 2002
OGD / CDER
TORPHARM

Amendment to ANDA #76-151
Diltiazem CD Capsules
(Diltiazem Hydrochloride Extended-Release Capsules USP)
120 mg, 180 mg, 240 mg and 300 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

formulation

Redacted 1

Page(s) of trade secret and /or confidential commercial information