CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75124

BIOEQUIVALENCE REVIEW(S)

Diltiazem HCl XR Capsules
120 mg, 180 mg and 240 mg
ANDA #75-124
Reviewer: A.P.Patel
Biofinal:75124sdw.997

Mylan, Inc.
Morgantown, WV
Submission Date:
Sept. 9, 1997

Review of 4 In Vivo Bioequivalence Studies, 2 Waiver Requests and Dissolution Data

I. Objective:

The firm submitted three bioequivalence studies and dissolution data to assess the bioequivalence of the Mylan's Diltiazem HCl Extended-Release (XR) Capsules, 240 mg, to Rhone-Poulenc Rorer's Dilacor XR® 240 mg Capsules. The firm requested a waiver of the in vivo bioequivalence testing requirements for its 120 mg and 180 mg strengths. To support the requests, the firm has submitted comparative dissolution profiles for its Diltiazem HCl Extended Release, 120 mg and 180 mg Capsules versus Dilacor XR® 120 mg and 180 mg Capsules, respectively. The formulations for the drug products Diltiazem HCl Extended-Release 120 mg, 180 mg and 240 mg Capsules are also submitted.

The following studies were performed and included in the submission:

1. Study #Dilt9631
A two-way crossover, single-dose bioequivalence study of Diltiazem HCl extended-release (XR) 240 mg Capsules under fasting conditions.

2. Study #Dilt9632
A three-way crossover, single-dose, post-prandial bioequivalence study of Diltiazem HCl XR 240 mg Capsules.

3. Study #Dilt9633
A two-way crossover, multiple-dose bioequivalence study of Diltiazem HCl XR 240 mg Capsules.

II. Background:

Diltiazem HCl is a calcium ion influx inhibitor. It is well-absorbed from the gastrointestinal tract, and undergoes an extensive first-pass effect. When given as an immediate release oral formulation, the absolute bioavailability of diltiazem is approximately 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. The plasma elimination half-life of diltiazem is approximately 3 to 4.5 hours. The apparent steady-state half-life of diltiazem following once-daily administration of Diltiazem Extended-Release Capsules ranges from 5 to 10 hours. This prolongation of half-life is attributed to continued absorption

of diltiazem rather than to alterations in its elimination. Diltiazem is metabolized by three major pathways into various metabolites. These pathways are I) O-demethylation, ii) Desacetylation (DAD) and N-monodemethyldiltiazem (NMD). Desacetyldiltiazem and N-monodemethyldiltiazem are active metabolites. At one time, Desacetyldiltiazem was thought to be the major metabolite of diltiazem, which is also present in the plasma at concentrations of 10% to 20% of the parent drug. It is approximately 25% to 50% as potent a coronary vasodilator as diltiazem. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

Diltiazem HCl is commercially available as oral tablets, extended-release capsules, and dual-release capsules. Each extended-release diltiazem HCl capsule (Dilacor XR^R, Rhone-Poulenc Rorer) consists of multiple 60-mg tablets contained in a swellable matrix core that slowly releases the drug over approximately 24 hours.

Simultaneous administration of Dilacor XR^R with a high-fat breakfast had a modest effect on diltiazem bioavailability with AUC increasing by 13% and Cmax by 37%. Therefore, Dilacor XR^R Capsules should be taken on empty stomach. Dosage must be adjusted to each patient's needs, starting with 180 mg or 240 mg once-daily.

III. Study #DILT9631 For Single-dose Fasting Bioequivalence Study:

Study site:

Analytical site: Mylan Pharmaceuticals, Inc.
Morgantown, WV
Analytical Project Leader:
Sandra Tarr

Study design: A randomized, single-dose, open-label, 2-way crossover bioequivalence study under fasting conditions in healthy male volunteers.

Study dates: Group A - Period I, October 5 - 8,1996
Period II, October 19 - 22,1996

Group B - Period I, October 21 - 24,1996
Period II, November 4 - 7,1996

Analysis: October 28, 1996 - December 2, 1996

Repeat, Confirmatory Study- Period 1:Jan. 19 -22, 1997
Period 2:Feb. 2 - 5, 1997

Analysis: February 10 - 13, 1997

Subjects: Thirty-two (32)healthy, non-smoking, adult male volunteers were enrolled in the study. All met the selection and exclusion criteria described in the protocol. They were judged to be healthy based on medical history, physical examination and clinical laboratory tests prior to period 1 dosing. All subjects were within 18 to 45 years of age and the weight range was not more than ± 10% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: A. 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Mylan), lot #2C004H, lot size capsules, manufacturing date 9/10/96. Content uniformity and potency are 98.8% (%CV=1.2) and 97.8%, respectively.

Reference product: B. 1x240 mg Dilacor XR^{R} Capsules (Rhone-Poulenc Rorer), lot #N54506, Exp. 5/98. Content uniformity and potency are 101.4% (%CV=1.7) and 101.9%, respectively.

All subjects received treatments with 240 ml of water at ambient temperature.

Subjects were dosed in two groups, Group A was #s 1 - 15 and Group B was #s 16 - 32.

Food and fluid intake: Following drug administration, the subjects remained fasting for 5 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. Water was permitted ad lib. until 2 hour before dosing and 2 hours after dosing.

Blood collection: Blood samples (10 ml) were drawn into Vacutainers prior to drug administration

(pre-dose) and at the following times after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 24, 32, 36 and 48 hours. Plasma was extracted and stored in labeled tubes at -20°C or lower until shipment. Sitting blood pressure and PR interval from Lead II ECGs monitored pre-dosing and hourly post-dosing at times indicated above.

Washout period: Two week.

Assay Methodology: Plasma samples were analyzed for diltiazem,

Statistical Analysis:

AUCT, AUCinf, Cmax, Kel, T1/2 and concentrations at each sampling time point were determined for diltiazem, desacetyldiltiazem and desmethyldiltiazem. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for lnAUCt, lnAUCinf and lnCmax.

IV. In Vivo Results:

Thirty-two (32) subjects enrolled in the study and completed the study. Subject 32 was outside the protocol age limits of 18 - 45; he was 46 at period 1 dosing. This deviation was not found until after dosing therefore subject 32 is not included in the data due to protocol violation. Data for subject #30 not available due to interferences. Subject 22 is considered as an outlier by statistical analysis and his data are not included in the analysis. Statistical analysis was performed on 29 out of 32 subjects who completed the study.

Pharmacodynamic data:
The firm has also collected pharmacodynamic data, heart rate, P-R interval, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and

reference are similar. The data were statistically analyzed using SAS-GLM repeated measures ANOVA. There was no clinically significant treatment difference in either the diastolic or systolic blood pressure, P-R interval or in the heart rate data for this study.

Adverse Events:
Sixteen adverse events were reported in thirteen of the thirty-one subjects dosed over the course of the study. The adverse events were assessed as probably (15) or possibly (1) drug related by the clinician. No subjects dropped or were withdrawn due to medical events. There were no serious or life threatening adverse events reported. There were no adverse events reported for the repeat, confirmatory study.

The plasma concentrations and pharmacokinetic parameters for diltiazem, desacetyldiltiazem and desmethyldiltiazem are summarized below.

Table I

Mean Plasma Diltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting Conditions

	TEST			REFERENCE			
Time (h)	N	Mean (ng/ml)	CV	N	Mean (ng/ml)	CV	Ratio (T/R)
0	28	0	.	29	0	.	
1	29	17.1	64.1	29	13.7	89.2	1.2
2	28	40.6	53.3	29	36.9	59.1	1.1
3	29	55.8	38.6	29	49.8	51.8	1.1
4	29	58.5	38.7	29	51.5	49.9	1.1
5	29	58	39.7	29	52.7	55.1	1.1
6	29	59.3	39.1	29	57.5	52.5	1.0
7	29	54.1	38.5	29	56.8	56.8	1.0
8	29	54.3	41.1	29	56.9	52.9	1.0
9	29	52.5	39.4	29	57.3	49.7	0.9
10	29	52.2	42.2	29	57.1	52.8	0.9
11	29	55.5	42.8	29	63	48.9	0.9
12	29	52.8	47.5	29	60.3	48.5	0.9
14	29	48.2	45.5	29	56.7	54	0.9
16	29	43.3	47	29	54.6	57.9	0.8
18	28	37.8	51.1	29	47.2	62.9	0.8
20	29	34	55.7	29	41.8	59.3	0.8
24	29	31.2	60.4	29	37.5	61.8	0.8
32	29	15.1	75.3	29	16.9	88.9	0.9
36	29	9.3	92	29	10.2	100.6	0.9
48	29	2.2	168.8	29	2.7	157.1	0.8
							Ratio (T/R)
AUCT	29	1347.7	42.5	29	1491.6	55.2	0.9
AUCI	29	1396.9	43.6	29	1550	55.2	0.9
CMAX	29	73.5	33.6	29	75.1	42.8	1.0
TMAX	29	8.2		29	10.4		0.8
KEL	29	0.1		29	0.1		1.0
THALF	29	6.3		29	6.3		1.0
							90% CI
LAUCT		7.1			7.2		83 - 106%
LAUCI		7.1			7.2		83 - 107%
LCMAX		4.2			4.2		89 - 114%

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

Data of 29 subjects are analyzed. Subject #30's data were not obtainable due to interferences and subject #32 deviated from the protocol and his data were not analyzed.

Subject 22 had lower diltiazem and desacetyldiltiazem plasma concentrations with test and reference products with respect to mean concentrations. The firm has determined subject #22's desacetyldiltiazem plasma data as statistical outlier and not included in the analysis. To verify subject 22's data as aberrant from the original study, the firm has conducted a separate repeat confirmatory study (DILT-9631A) for subject# 22 accompanied by subject# 19 and 24. The diltiazem and desacetyldiltiazem pharmacokinetic parameters for the confirmatory study and the original study are reviewed below.

1. For Diltiazem (without subject #22 data), the 90% confidence intervals for AUCT, AUCI and Cmax are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

	without subject #22	with subject #22
	90% CI	90% CI
LAUCT	82.8 - 106.1%	79.6 - 104.5
LAUCI	82.6 - 107.2%	79.5 - 103.6
LCMAX	89.3 - 114.2%	85.5 - 111.3

2. The Diltiazem mean plasma levels peaked at 6 and 11 hours for the test and the reference products, respectively, under fasting conditions.

Table II

Mean Plasma Desacetyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting Conditions

	Test			Reference			Ratio
Time (h)	N	Mean (ng/ml)	CV	N	Mean (ng/ml)	CV	(T/R)
0	28	0	.	29	0	.	
1	29	0.2	311.3	29	0.3	233.7	0.7
2	28	1.6	80.3	29	1.3	99.7	1.2
3	29	2.9	52.1	29	2.4	65.8	1.2
4	29	3.7	51	29	3.2	56.1	1.2
5	29	4.4	44.1	29	3.9	57.4	1.1
6	29	5.2	50.3	29	4.9	63.5	1.1
7	29	5.4	50.2	29	5.2	61.9	1.0
8	29	5.9	52.3	29	5.7	63.6	1.0
9	29	6.1	55.3	29	6.3	65.9	1.0
10	29	6.5	55.1	29	6.7	70.5	1.0
11	29	7	60.3	29	7.6	77.9	0.9
12	29	7.3	59.5	29	8	78.1	0.9
14	29	7.6	64.2	29	8.5	79.8	0.9
16	29	7.9	71.8	29	9.2	83.9	0.9
18	28	7.8	73.2	29	8.7	88.2	0.9
20	29	8	81.2	29	9	91.6	0.9
24	29	8.2	89.4	29	9.4	99.3	0.9
32	29	6.8	115.8	29	7	120.5	1.0
36	29	4.7	127.2	29	4.8	128.5	1.0
48	29	2	158.9	29	2	148.6	1.0
							Ratio (T/R)
AUCT	29	265.4	88.1	29	283.4	96.4	0.9
AUCI	27	336.6	87.5	26	359	88.5	0.9
CMAX	29	9.9	71.6	29	10.8	86	0.9
TMAX	29	17.7		29	18.2		1.0
KEL	27	0.1		26	0.1		1.0
THALF	27	11.1		26	10.9		1.0
							90% CI
LAUCT	29	5.2		29	5.2		83 - 109%
LAUCI	27	5.5		26	5.5		84 - 111%
LCMAX	29	2.1		29	2.1		86 - 109%

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

Data from 29 subjects were analyzed (please see under diltiazem for explanation).

1. For Desacetyldiltiazem, the ln-least squares means for AUCT, AUCI and Cmax values were same for the test and the reference products. The 90% confidence intervals (without subject #22's data) for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

	without subject #22	with subject #22
	90% CI	90% CI
LAUCT	83.0 - 108.8	76.6 - 105.6
LAUCI	84.2 - 110.6	79.5 - 107.3
LCMAX	85.9 - 108.8	83.0 - 106.4

2. The Desacetyldiltiazem plasma levels peaked at 16 hours for both the test and the reference products, under fasting conditions.

Table III

Mean Plasma Desmethyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting Conditions

	Test			Reference			
Time (h)	N	Mean (ng/ml)	CV	N	Mean (ng/ml)	CV	(T/R)
0	28	0	.	29	0	.	
1	29	3.1	83.6	29	2.5	102.1	1.2
2	28	9.5	40.4	29	9.2	46.5	1.0
3	29	14.4	26.6	29	12.8	36.2	1.1
4	29	16.2	32.9	29	14.3	33.9	1.1
5	29	16.3	31	29	14.6	33.2	1.1
6	29	18.2	33	29	16.7	33.9	1.1
7	29	18.1	30.4	29	17.5	35.5	1.0
8	29	17.9	30.2	29	18	36.9	1.0
9	29	17.9	29.5	29	18.4	36.9	1.0
10	29	17.8	30.7	29	18.5	36.6	1.0
11	29	18.4	29.9	29	19.6	37.4	0.9
12	29	18.2	31.1	29	19.9	34	0.9
14	29	17.5	29.6	29	19.3	34.9	0.9
16	29	16.6	30.9	29	19.5	36.4	0.9
18	28	15.5	33.5	29	18	38.5	0.9
20	29	14.1	35.3	29	16.5	39.6	0.9
24	29	12.3	40.3	29	14.5	41.9	0.8
32	29	8.6	56.2	29	9.9	56.2	0.9
36	29	6	64.6	29	6.8	67.5	0.9
48	29	1.7	135.3	29	2.1	131.3	0.8
							Ratio (T/R)
AUCT	29	507.5	31.8	29	555.8	41.3	0.9
AUCI	29	558.4	31.7	29	615.7	40.5	0.9
CMAX	29	21	23.5	29	22.3	30.4	0.9
TMAX	29	9.8		29	12.3		0.8
KEL	29	0.1		29	0.1		1.0
THALF	29	8.8		29	9.2		1.0
							90% CI
LAUCT	29	6.2		29	6.2		1.0 84 - 104%
LAUCI	29	6.3		29	6.3		1.0 84 - 102%
LCMAX	29	3		29	3.1		1.0 88 - 105%

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

Data from 29 subjects were analyzed (please see under diltiazem for explanation).

1. For Desmethyldiltiazem, the ln-least squares means for AUCT, AUCI and Cmax are similar for the test and the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

	without subject #22 90% CI	with subject #22 90% CI
LAUCT	84.0 - 104.2%	81.3 - 102.0
LAUCI	83.9 - 102.3%	81.4 - 100.3
LCMAX	88.0 - 104.5%	85.4 - 102.7

2. The Desmethyldiltiazem plasma levels peaked at 11 hours for the test and at 12 hours for the reference product, under fasting conditions.

IV. Study #Dilt9631A For Single-dose Bioequivalence under fasting conditions Study of Diltiazem HCl 240 mg XR Capsules

Subject 22 had lower diltiazem and desacetyldiltiazem plasma concentrations with test and reference products with respect to mean concentrations. The firm has determined subject #22's desacetyldiltiazem plasma data as statistical outlier and not included in the original analysis. To verify subject 22's data as aberrant from the original study, a separate repeat confirmatory study (DILT-9631A) for subject# 22 accompanied by subject# 19 and 24 was conducted.

The objective of this study was to verify subject #22's response in a repeat confirmatory study. Subject 22 and subjects #19 and #24 were redosed under fasting conditions with a single dose of Diltiazem HCl XR 240 mg Capsules (Mylan) and Dilacor XR^{R} 240 mg Capsules (Rhone-Poulenc Rorer Pharmaceuticals Inc.). The conduct of repeat, cofirmatory study was identical to the original study and conformed to the protocol. The subjects were dosed in the same sequence in the repeat study as in the original study.

Study site and analytical site are as described for study #Dilt9631.

Study design:	Single-dose, two-way crossover, bioequivalence study under fasting conditions.
Study dates:	Period 1, October 5 - 8,1996 Period 2, October 19 - 22,1996

Analysis: November 25, 1996 - December 18, 1996

Subjects:	Three (3) healthy, non-smoking, adult male volunteers ages 18-45 were redosed. All met the selection and exclusion criteria described in the protocol. No subjects withdrew or were withdrawn from the study.
Dose and treatment:	All subjects completed an overnight fast (9.5 hours) before any of the following drug treatments:

Test product: A. 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Mylan), lot #2C004H, administered following an overnight fast.

Reference product: B. 1x240 mg Dilacor XR^{R} Capsules (Rhone-Poulenc Rorer), lot #N54506, administered following an overnight fast.

Food and fluid intake: Following drug administration, the subjects remained fasting for 5 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. Water was permitted ad lib. until 2 hour before dosing and 2 hours after dosing.

Blood collection: Blood samples (10 ml) were drawn into Vacutainers prior to drug administration (pre-dose) and at the following times after dosing: 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 24, 32, 36 and 48 hours. Plasma was extracted and stored in labeled tubes at -20°C or lower until shipment. Sitting blood pressure and PR interval from Lead II ECGs monitored pre-dosing and hourly post-dosing at times indicated above.

Washout period: Two week.

Assay Methodology: Similar specifications to Study #Dilt9631 above.

Data Analysis:

Cmax for diltiazem, desacetyldiltiazem and desmethyldiltiazem was determined by establishing the peak concentration for each subject. The areas under the plasma diltiazem, desacetyldiltiazem and desmethyldiltiazem concentration versus time curves (AUCs) were calculated by using the linear trapezoidal rule.

In Vivo Results:

Three (3) subjects were enrolled in the study and all subjects completed the study. Pharmacokinetic parameters were compared with those in the original study (Dil#9631). The subjects were dosed in the same sequence in the repeat study as the original study.

Pharmacodynamic data:
The firm has also collected pharmacodynamic data, heart rate, P-R interval, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and reference are similar.

Adverse Events: none

The plasma concentrations and pharmacokinetic parameters for diltiazem, desacetyldiltiazem and desmethyldiltiazem are summarized below for the repeat confirmatory study (Dil#9631A).

Table IV

Mean Plasma Diltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting Conditions

	Test			Reference			Ratio
Time(h)	N	Mean	CV	N	Mean	CV	(T/R)
0	3	0	.	3	0	.	.
1	3	16.1	99.2	3	6.2	34.9	.
2	3	43.5	6.6	3	31.7	35.2	1.4
3	3	51	44.9	3	36.8	40.5	1.4
4	3	55.2	38.8	3	40	50.5	1.4
5	3	59.5	55.5	3	40.4	47.1	1.5
6	3	62.6	56.1	3	49.1	14.5	1.3
7	3	55.6	55	3	50.2	14.5	1.1
8	3	52.9	60.6	3	43.4	4.9	1.2
9	3	43.5	59.3	3	42.2	25.6	1.0
10	2	25.6		3	38.1	37	0.7
11	3	38.1	36.3	3	44.3	55.2	0.9
12	3	34.8	24.5	3	41.6	51.5	0.8
14	2	42		3	38.8	62.1	1.1
16	3	39.5	43.6	3	38.2	70.3	1.0
18	3	35.8	46.4	3	35	77.6	1.0
20	3	35.1	66.8	3	30.4	73.9	1.2
24	3	36.7	69.6	3	29.5	78.3	1.2
32	3	23.9	70.1	3	12.3	86.7	1.9
36	3	11.6	68.1	3	7.4	90.1	1.6
48	3	3.2	95.4	3	1.1	173.2	.
AUCT	3	1372.4	22.1	3	1094.2	51.7	1.3
AUCI	3	1408.1	22.8	3	1138.6	51.8	1.2
CMAX	3	68	46.4	3	58.5	22.1	1.2
TMAX	3	16.7	56.7	3	14	63.5	1.2
KEL	3	0.1	13.9	3	0.1	9.2	1.0
THALF	3	6.1	12.8	3	5.9	8.9	1.0
LAUCT	3	7.2	3	3	6.9	9.5	1.0
LAUCI	3	7.2	3.1	3	6.9	9.4	1.0
LCMAX	3	4.1	11.1	3	4.1	5.5	1.0

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

The diltiazem plasma levels peaked at 6 and 7 hours for the test and the reference products,respectively, under fasting conditions.

Comparison of diltiazem PK parameters from Original and repeat studies:

Diltiazem Original Study Data

	Test				Reference		
SUB	CMAX	AUCT	AUCI	SUB	CMAX	AUCT	AUCI
19	52.2	1313	1336.2	19	61.4	1666.5	1699.5
22	15.4	199.3	215.2	**22**	42.3	610.7	659.5
24	87.3	1012.1	1059.6	24	66.4	733.2	760.6
Mean	51.6	841.5	870.3		56.7	1003.5	1039.9
CV	69.6	68.5	67.1		22.4	57.5	55.2

Diltiazem Repeat study Data

	Test				Reference		
SUB	CMAX	AUCT	AUCI	SUB	CMAX	AUCT	AUCI
19	41	1289.8	1316.1	19	71.8	1539.6	1619.8
22	60.3	1707.9	1765.1	**22**	45.9	1285.7	1315
24	102.7	1119.6	1143.3	24	57.7	457.2	480.9
Mean	68.0	1372.4	1408.2		58.5	1094.2	1138.6
CV	46.4	22.1	22.8		22.2	51.7	51.8

Subject #22's PK parameters in the repeat study are similar to mean parameters from the original study. Original data appears to aberrant in nature and were excluded.

Table V

Mean Plasma Desacetyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting Conditions

	Test			Reference			Ratio
Time(h)	N	Mean	CV	N	Mean	CV	(T/R)
0	3	0	.	3	0	.	.
1	3	0	.	3	0	.	.
2	3	1.9	25.7	3	1.1	96.7	1.7
3	3	2.6	71.8	3	2.2	31	1.2
4	3	3.3	61.5	3	2.7	28.6	1.2
5	3	4.7	62.7	3	3.2	14.5	1.5
6	3	5.6	74.1	3	4.4	35.3	1.3
7	3	5.8	84.9	3	5.6	75.3	1.0
8	3	6.1	87.8	3	5.6	69.5	1.1
9	3	6.1	93.1	3	5.8	74.2	1.1
10	2	2.6		3	6	71.9	0.4
11	3	6.3	98.8	3	6.3	64.7	1.0
12	3	5.5	99.1	3	5.5	68.1	1.0
14	2	3.1		3	6	43.1	0.5
16	3	6.2	68.6	3	5.9	34	1.1
18	3	5.8	66.8	3	5.3	31.5	1.1
20	3	5.7	60.6	3	5.2	21.2	1.1
24	3	6.6	27.9	3	5.4	8.7	1.2
32	3	5	30.5	3	3.1	16.5	1.6
36	3	3.5	35.1	3	2.2	22.6	1.6
48	3	1.5	37.7	3	0	.	.
AUCT	3	215.7	54	3	156.8	27.3	1.4
AUCI	2	263.8		2	206		1.3
CMAX	3	8.3	56.3	3	7.7	38.5	1.1
TMAX	3	19.7	38.2	3	16.7	42.1	1.2
KEL	2	0.1		2	0.1		1.0
THALF	2	9		2	9.3		1.0
LAUCT	3	5.3	9.5	3	5	5.5	1.1
LAUCI	2	5.5		2	5.3		1.0
LCMAX	3	2	26.2	3	2	18.5	1.0

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

The desacetyldiltiazem plasma levels peaked at 11 hours for the test and the reference products, under fasting conditions.
Comparison of desacetyldiltiazem PK parameters from Original and repeat studies:

Desacetyldiltiazem Original Study Data

	Test				Reference		
SUB	CMAX	AUCT	AUCI	SUB	CMAX	AUCT	AUCI
19	5.0	135.7	191.3	19	6.0	150.5	200.0
22	1.5	13.6	31.6	**22**	3.5	77.3	106.8
24	11.9	350.5	387.9	24	10.6	262.7	283.6
Mean	6.1	166.6	203.6		6.7	163.5	196.8
CV	86.3	102.4	87.7		53.8	57.1	44.9

Desacetyldiltiazem Repeat Study Data

	Test				Reference		
SUB	CMAX	AUCT	AUCI	SUB	CMAX	AUCT	AUCI
19	5.0	136.6	149.4	19	6.7	153.5	169.9
22	6.3	161.2	.	**22**	5.3	115.7	.
24	13.6	349.4	378.3	24	11.0	201.2	242.1
Mean	8.3	215.7	263.9		7.7	156.8	206.0
CV	55.9	54.0			38.7	27.3	

Subject #22's PK parameters in the repeat study are similar to mean parameters from the original study. Original data appears to aberrant in nature and were excluded.

Table VI

Mean Plasma Desmethyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting Conditions

	Test			Reference			Ratio
Time(h)	N	Mean	CV	N	Mean	CV	(T/R)
0	3	0	.	3	0	.	.
1	3	2.4	96	3	0	.	.
2	3	11	12.1	3	8.9	28.1	1.2
3	3	13.2	45.7	3	11	27.4	1.2
4	3	14.3	32.7	3	11.7	33.4	1.2
5	3	15.2	46.4	3	12.1	37.5	1.3
6	3	16.2	45.4	3	13.9	27.5	1.2
7	3	15.7	38.4	3	14.5	20.9	1.1
8	3	15.7	41	3	14.1	16.6	1.1
9	3	14.5	46.2	3	13.7	30.1	1.1
10	2	10.3	6.9	3	13	31	0.8
11	3	13.8	40.3	3	14.1	42.1	1.0
12	3	13.2	38	3	14.4	41.4	0.9
14	2	13.3	5.7	3	13.9	49.9	1.0
16	3	13.6	6.3	3	14.1	57.3	1.0
18	3	13.3	9.9	3	14.1	65.6	0.9
20	3	12.5	25.6	3	12.6	62.6	1.0
24	3	12	33.8	3	11.3	64.9	1.1
32	3	10.5	45	3	7.4	73	1.4
36	3	6.8	48.1	3	5	87.9	1.4
48	3	2.4	86.8	3	1.6	87.2	1.5
AUCT	3	482.5	11.5	3	430.5	53.6	1.1
AUCI	3	531.9	9.4	3	458.9	49.5	1.2
CMAX	3	18.2	31.1	3	16.5	38	1.1
TMAX	3	14	51.5	3	15	46.7	0.9
KEL	3	0.1	14.9	3	0.1	23.8	1.0
THALF	3	9.7	15.5	3	8.9	23.8	1.1
LAUCT	3	6.2	1.9	3	5.9	10.4	1.1
LAUCI	3	6.3	1.5	3	6	9.2	1.1
LCMAX	3	2.9	10.2	3	2.8	12.9	1.0

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

The desmethyldiltiazem plasma levels peaked at 6 and 7 hours for the test and the reference products,respectively, under fasting conditions.

Subject #22's PK parameters in the repeat study are similar to mean parameters from the original study. Original data were not aberrant in nature.

V. Study #Dilt9633, Multiple-dose Bioequivalence Study of Diltiazem HCl 240 mg XR Capsules

The objective of the study was to assess the bioavailablity at steady-state of Diltiazem HCl 240 mg XR Capsules (Mylan) as compared to Dilacor XR^R 240 mg Capsules (Rhone-Poulenc Rorer Pharmaceuticals Inc.) following once-a-day dosing of each formulation for six days, under fasting conditions.

Study and analytical sites were described for Dilt9631 above.

Study design: A randomized, multiple-dose, 2-way crossover bioequivalence study under fasting conditions.

Study dates: Period I, November 21-28, 1996
Period II, December 13-20, 1996

Analysis dates: December 23, 1996 - January 27, 1997.

Subjects: Thirty-four (34) healthy male volunteers were enrolled in the study. All subjects met the selection and exclusion criteria described in the protocol as outlined for study Dilt9631 above.
Thirty (30) subjects completed the study.

Dose and treatment: All subjects completed an overnight fast (10 hours) prior to dose administration until at least 5 hours after dosing during each study period.

Test product: A. Days 1-6: 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Mylan), lot #2C004H. The single oral dose was administered with 240 ml of water following a 10 hour overnight fast.

Reference product: B. Days 1-6: 1x240 mg Dilacor XR^R Capsules (Rhone-Poulenc Rorer), lot #N54506. The single oral dose was administered with 240 ml of water following a 10 hour overnight fast.

Blood collection: Serial blood samples (1x10ml) before dosing on Day 1 and following the sixth dose at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20 and 24 hours. Trough levels were also taken prior to dosing on Day 4 (-48 hours), Day 5 (-24 hours) and Day 6 (0 hours). Plasma samples were stored at -70°C ± 15°C until shipment for analysis.

Subject monitoring: **The subjects were monitored throughout the confinement portion of the study. Sitting blood pressure, pulse and Lead II ECGs were measured before the sixth dose and hourly after the sixth dose for the first twelve hours and at 24 hours. For safety, these vital signs were measured hourly for the first twelve hours after the first dose and before each morning dose on Day 1 through Day 6.**

Washout period: **Two week.**

Assay Methodology: Same as Study #Dilt9631 above.

Statistical Analysis:

AUC_{0-T}, Cmax, Cmin, Tmax, Flux and concentrations at each sampling time point were determined for diltiazem, desacetyldiltiazem and desmethyldiltiazem. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for lnAUC_{0-T} and lnCmax.

VI. In Vivo Results:

Thirty-four (34) subjects enrolled in the study. Subject #5 was not dosed due to an elevated temperature before Period 1 dosing. Subject #7 was discontinued due to an adverse event in Period 1 which was not drug related. Subject #21 dosed with reference was withdrawn during Period 1 due to an asymptomatic second degree heart block. Subject #18 did not report for personal reasons which were not study related. Thirty (30) subjects completed the study.

Pharmacodynamic data:
The firm has also collected pharmacodynamic data, heart rate, P-R interval, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and reference are similar. The data were statistically analyzed using SAS-GLM repeated measures ANOVA. There was no clinically significant treatment difference in either the diastolic or systolic blood pressure, P-R interval or in the heart rate data for this study.

Adverse Events: There were 19 adverse events reported in 11 out of 30 subjects dosed. Of those, 15 were listed as probably or possibly drug related. Subject #21 was discontinued due to asymptomatic second degree heart block. Subject #7 was discontinued due to possibly drug related adverse event.

The plasma concentrations and pharmacokinetic parameters for

diltiazem, desacetyldiltiazem and desmethyldiltiazem are summarized below.

Table VII

Mean Diltiazem Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (240 mg for 6 days) of Diltiazem HCl XR Capsules

	Test-A			Reference- B			Ratio
Time (h)	N	Mean ng/ml	CV	N	Mean ng/ml	CV	(A/B)
-120	29	0	.	30	0	.	
-48	29	37.6	59.1	29	46.5	51.1	0.8
-24	30	46.3	56.7	30	52.9	43	0.9
0	30	42.8	48.1	30	40.6	53.7	1.1
1	30	71.9	41.3	30	63.5	48.3	1.1
2	30	101	39.3	30	93.5	39.6	1.1
3	30	119.1	41.3	30	104.8	35.6	1.1
4	30	111.9	42.4	30	102.7	41.7	1.1
5	30	104.1	41.7	30	101.1	42.9	1.0
6	30	99.2	47.9	30	99	45.5	1.0
7	30	90.3	45.8	30	91.8	44.8	1.0
8	30	85.3	43.7	30	89.8	41.3	0.9
9	30	82.3	43.5	30	89.3	40.1	0.9
10	30	79.7	44	30	88.3	43.8	0.9
11	30	78.2	44	30	86.8	45.4	0.9
12	30	73.2	43.6	30	85	44.9	0.9
14	30	67.1	47.3	30	74.3	46.2	0.9
16	30	59	46.4	30	66.2	50.2	0.9
18	30	47.7	50.8	30	54.5	54.6	0.9
20	30	42.1	49.2	29	46.8	61.6	0.9
24	30	37.5	52.5	30	41.8	63.6	0.9
							Ratio (A/B)
AUC	30	1703.1	39.5	30	1774.7	42.2	1.0
CMAX	30	126	37.1	30	119.9	36.3	1.1
Cmin	30	30.6	54.7	30	33.2	67.7	0.9
TMAX	30	4.5	74.3	30	5.7	62.5	0.8
FLUCT%*	30	141.7	29.8	30	131.5	42	1.1

* FLUCT%=((Cmax-Cmin)/Css)x100; Css=AUCT/24(dosing interval)

							90% CI
LAUC	30	7.4		30	7.4	1.0	86 - 113
LCMAX	30	4.8		30	4.7	1.0	94 - 117

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

1. The plasma Diltiazem levels peaked at 3 hours post dose on the sixth Day for the test and the reference products.

2. For diltiazem, the ln-least squares means for AUC(0-24) and Cmax values were similar for the test and reference products. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

Table VIII

Mean Desacetyldiltiazem Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (240 mg for 6 days) of Diltiazem HCl XR Capsules

	Treatment A			Treatment B			Ratio
Time (h)	N	Mean ng/ml	CV	N	Mean ng/ml	CV	(A/B)
-120	29	0	.	30	0	.	
-48	29	15.1	137.9	29	16	126.9	0.9
-24	30	15.1	121.5	30	17.2	118.2	0.9
0	30	15	112.5	30	15	125.4	1.0
1	30	15.7	110.3	30	15.7	121.4	1.0
2	30	17.4	100.3	30	17.3	111.2	1.0
3	30	19.1	95.6	30	17.8	107.4	1.1
4	30	19.4	94.5	30	18.4	102.8	1.1
5	30	19.7	96.4	30	18.9	103.9	1.0
6	30	20	95.5	30	19.1	102.3	1.0
7	30	19.7	100.7	30	18.9	103.1	1.0
8	30	19.9	103.8	30	19	105	1.0
9	30	20	109.2	30	19.4	107.2	1.0
10	30	20.3	115	30	19.4	109.6	1.0
11	30	19.3	121.3	30	18.9	111.4	1.0
12	30	19.4	121.5	30	19.7	111.8	1.0
14	30	19.1	134	30	18.5	110.5	1.0
16	30	18.1	136.6	30	18	121.6	1.0
18	30	16.3	138	30	16.4	125.2	1.0
20	30	16.3	145.8	30	15.8	130.2	1.0
24	30	16.1	158.2	30	15.6	141.1	1.0
							Ratio (A/B)
AUCT	30	435.1	120.3	30	424.5	115.2	1.0
CMAX	30	24.1	112	30	22.2	99.8	1.1
Cmin	30	12.3	136.3	30	13.2	139.2	0.9
TMAX	30	8.5	70.9	30	8.7	55.8	1.0
FLUCT%*	30	79.5	35.5	30	76.3	58.8	1.0

* FLUCT%=((Cmax-Cmin)/Css)x100; Css=AUCT/24(dosing interval)

						90% CI
LAUCT	30	5.7	30	5.6	1.0	89 - 120
LCMAX	30	2.8	30	2.8	1.0	92 - 121

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

1. The plasma Desacetyldiltiazem levels peaked at 10 and 12 hours post dosing on the sixth day for the test and the reference products, respectively.

2. For Desacetyldiltiazem, the ln-least squares means for AUC(0-24) and Cmax values were similar for the test and the reference product. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

Table IX

Mean Desmethyldiltiazem Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (240 mg for 6 days) of Diltiazem HCl XR Capsules

	Treatment A			Treatment B			Ratio	
Time (h)	N	Mean ng/ml	CV	N	Mean ng/ml	CV	Mean (A/B)	
-120	29	0	.	30	0	.		
-48	29	17.3	47.3	29	19.8	38	0.9	
-24	30	18.8	39.2	30	21.3	36.2	0.9	
0	30	18	42.8	30	18.1	41.9	1.0	
1	30	22.1	34.2	30	21.4	39.5	1.0	
2	30	27.5	32.8	30	26.5	32.9	1.0	
3	30	30.8	33	30	29.6	29.3	1.0	
4	30	31.2	34.2	30	29.6	31.4	1.1	
5	30	30.4	34.1	30	29.8	31.7	1.0	
6	30	29.8	35.9	30	29.7	33.1	1.0	
7	30	30.6	38.5	30	29.8	32.7	1.0	
8	30	30.1	37.4	30	30.2	32.5	1.0	
9	30	29.9	38.8	30	30.4	32.3	1.0	
10	29	28.1	38.4	30	30	33.1	0.9	
11	30	28.4	39.7	30	29.7	35.7	1.0	
12	30	27.5	36.3	30	29.7	33.6	0.9	
14	30	25.9	38.1	30	27.6	35.5	0.9	
16	30	24.3	39.3	30	26	38.9	0.9	
18	30	20.5	41.4	30	22.8	41.1	0.9	
20	30	18.8	39.9	30	20.4	45.1	0.9	
24	30	16	41.8	30	17.7	46.6	0.9	
							Ratio (T/R)	
AUCT	30	599.7	34.5	30	619.8	33.9	1.0	
CMAX	30	34.3	33.2	30	34.1	27.4	1.0	
TMAX	30	6.5	61.8	30	7.2	58.3	0.9	
Cmin	30	14.1	45	30	15.4	49.1	0.9	
FLUCT%*		30	83.8	29.9	30	81.3	47.3	1.0

* FLUCT%=((Cmax-Cmin)/Css)x100; Css=AUCT/24(dosing interval)

						90% CI
LAUCT	30	6.3	30	6.4	1.0	88 - 109
LCMAX	30	3.5	30	3.5	1.0	91 - 109

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

1. The plasma Desmethyldiltiazem levels peaked at 4 hours and 9 hours post dose on sixth Day for the test and the reference products, respectively.

2. For Desmethyldiltiazem, the ln-least squares means for AUC(0-24) and Cmax values were similar for the test and the reference product. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

VII. Study #Dilt9632 For Single-dose Post Prandial Bioequivalence Study of Diltiazem HCl 240 mg XR Capsules

The objective of this study was to evaluate the effect of food on the rate and extent of absorption of a single dose of Diltiazem HCl XR 240 mg Capsules (Mylan) relative to Dilacor XR^R 240 mg Capsules (Rhone-Poulenc Rorer Pharmaceuticals Inc.)

Study site and analytical site are as described for study #Dilt9631.

Study design: Single-dose, three-way crossover, post-prandial bioequivalence study.

Study dates: Group A - Period 1, October 5 - 8,1996
Period 2, October 19 - 22,1996
Period 3, October 23 - 26,1996

Group B - Period 1, October 9 - 12,1996
Period 2, October 23 - 26,1996
Period 3, November 6 - 9,1996

Analysis: November 25, 1996 - December 18, 1996

Subjects: Twenty (20) healthy, non-smoking, adult male volunteers ages 18-45 were accepted in the study. All met the selection and exclusion criteria described in the protocol. No subjects withdrew or were withdrawn from the study.

Dose and treatment: All subjects completed an overnight fast (9.5 hours) before any of the following drug treatments:

A. 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Mylan), lot #2C004H, administered within 30 minutes of a high fat breakfast preceded by an overnight fast.

B. 1x240 mg Dilacor XR^{R} Capsules (Rhone-Poulenc Rorer), lot #N54506, administered within 30 minutes of a high fat breakfast preceded by an overnight fast.

C. 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Mylan), lot #2C004H, administered following an overnight fast.

Food and fluid intake: Following drug administration, the subjects remained fasting for 5 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. No fluid except that given with the standardized breakfast (1 fried egg, 1

serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 240 ml ounces of whole milk and 180 ml ounces of orange juice) and with drug administration water was allowed ad lib from 2 hour prior to dose administration until 2 hours after dosing.

Blood collection: Blood samples (10 ml) were drawn into Vacutainers prior to drug administration (pre-dose) and at the following times after dosing: 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 24, 32, 36 and 48 hours. Plasma was extracted and stored in labeled tubes at -20°C or lower until shipment. Sitting blood pressure and PR interval from Lead II ECGs monitored pre-dosing and hourly post-dosing at times indicated above.

Washout period: Two week.

Assay Methodology: Same as Study #Dilt9631 above.

Data Analysis:

Cmax for diltiazem, desacetyldiltiazem and desmethyldiltiazem was determined by establishing the peak concentration for each subject. The areas under the plasma diltiazem, desacetyldiltiazem and desmethyldiltiazem concentration versus time curves (AUCs) were calculated by using the linear trapezoidal rule.

VIII. In Vivo Results:

Twenty (20) subjects enrolled in the study all subjects completed the study. Statistical analysis was performed on all 20 subjects in the study.

Pharmacodynamic data:
The firm has also collected pharmacodynamic data, heart rate, P-R interval, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and reference are similar. The data were statistically analyzed using SAS-GLM repeated measures ANOVA. There was no clinically significant treatment difference in either the diastolic or systolic blood pressure, P-R interval or in the heart rate data for this study.

Adverse Events: Eight adverse events were reported in 6 out of 20 subjects. The adverse events did not require clinical intervention and were deemed as probably drug related. There were no serious or life-threatening adverse event reported.

The plasma concentrations and pharmacokinetic parameters for diltiazem, desacetyldiltiazem and desmethyldiltiazem are summarized below.

Table X

Mean Plasma Diltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting and Nonfasting Conditions

	Treatment A Mylan-Test Nonfasting			Treatment B Reference Nonfasting			Treatment C Mylan-Test fasting		Ratio
Time (h)	N	Mean ng/ml	CV	N	Mean ng/ml	CV	N	Mean ng/ml	CV	(A/B)
0	19	0	.	20	0	.	20	0	.	
1	20	0.3	307.8	19	1.2	144.7	20	9.4	51.9	0.3
2	20	10.9	78.1	19	15	82.7	20	26.9	42.5	0.7
3	19	36.2	57.1	20	38	55.1	20	38.4	51.6	1.0
4	19	49.6	44.4	20	43.7	54.1	19	36.6	45	1.1
5	19	60.9	40.2	19	53.5	49	20	37.8	50.8	1.1
6	20	93.7	47.1	20	76.5	38.2	20	38.8	55.6	1.2
7	19	87.4	46.2	20	74.5	39.2	20	37.8	50.9	1.2
8	19	86.4	39.9	20	72.5	37.9	19	34.3	50.4	1.2
10	20	76	34.1	20	79.2	30.2	20	36.4	53.8	1.0
12	20	68.3	37.5	19	75.5	55.8	20	38.1	65.2	0.9
14	20	58.9	33.6	19	61.1	50.2	20	36.7	72.3	1.0
16	20	52.9	34.5	19	55.4	44.9	20	36.4	69.3	1.0
20	20	36.7	35.8	20	43.9	41.4	20	27.9	62	0.8
24	19	30	41.5	20	34.5	40.7	20	25.9	60.5	0.9
30	20	17	63	19	17.7	49.9	20	17.5	67.8	1.0
36	20	6.8	109.4	20	6.6	63.1	19	8.3	97.7	1.0
48	20	1.1	259.4	19	1.1	144.2	19	2.7	117.9	1.0
		A			**B**			**C**		**Ratio A/B**
AUCT	20	1483.1	32.8	20	1520.2	33.3	20	1046.1	52.2	1.0
AUCI	20	1527.5	32.8	20	1557.1	32.6	20	1096.9	51	1.0
CMAX	20	105.3	40.9	20	102.2	32.7	20	51.9	47.8	1.0
TMAX	20	8.5		20	9.2		20	10.6		0.9
KEL	20	0.1		20	0.1		20	0.1		1.0
THALF	20	5.4		20	5.3		20	7		1.0

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

1. The diltiazem mean plasma levels peaked at 6 hours for the test product under fasting and nonfasting conditions and at 10 hours for the reference product under nonfasting condition.

2. For Mylan's test product, the mean AUCT, AUCI and Cmax values were 2.4% and 1.9% lower, and 3.0% higher, respectively, than the reference product values under nonfasting conditions. The mean AUCT, AUCI and Cmax values under fasting conditions are lower than under nonfasting conditions.

3. The ratios of the test to the reference arithmetic mean are within the acceptable range of 0.8-1.2 for AUCT, AUCI and Cmax.

Table XI

Mean Plasma desacetyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting and Nonfasting Conditions

	Treatment A Mylan-Test Nonfasting			Treatment B Reference Nonfasting			Treatment C Mylan-Test Fasting			Ratio
Time (h)	N	Mean ng/ml	CV	N	Mean ng/ml	CV	N	Mean ng/ml	CV	(A/B)
0.0	19	0	.	20	0	.	20	0	.	
1.0	20	0	.	19	0	.	20	0	.	
2.0	20	0.3	447.2	19	0.3	249.9	19	0.8	131.4	1.0
3.0	19	1.5	83.8	20	1.6	83.8	20	2	70.4	0.9
4.0	19	2.4	59.2	20	2.2	72.7	19	2.5	50.8	1.1
5.0	19	3.5	50.6	19	3.3	58.3	20	3.2	56.9	1.1
6.0	20	5.7	58	20	5	61.5	20	3.5	66.3	1.1
7.0	19	6.6	65.7	20	5.4	52.2	19	4.3	66.9	1.2
8.0	19	8	67.4	20	6.4	56.6	19	4	66.1	1.3
10.0	20	9.2	69.3	20	8.2	54.5	20	5.1	74.2	1.1
12.0	20	9.7	68	19	8.5	60.7	20	5.7	77.2	1.1
14.0	20	9.9	77.8	19	9.3	63	20	6.1	83.5	1.1
16.0	20	9.8	73.5	19	9.5	65.9	20	6.7	92	1.0
20.0	20	9.3	80.5	20	9.9	71.5	20	6.9	94	0.9
24.0	19	8.5	84	20	9.8	77.6	20	8	103.9	0.9
30.0	20	7.3	110.1	19	6.7	95.9	19	7.1	109	1.1
36.0	20	4.2	135.3	20	4.1	115.8	19	3.6	120.1	1.0
48.0	20	1.6	181	19	1.4	179.8	19	2.1	160.1	1.1

	A			B			C			Ratio (A/B)
AUCT	20	290.1	91.2	20	277.4	80.8	20	234.4	98.9	1.1
AUCI	19	338.8	92.8	20	312.4	80.9	17	257.9	92.6	1.1
CMAX	20	11.7	76.1	20	11.3	61.9	20	8.9	87.9	1.0
TMAX	20	16.2		20	17.1		20	20		1.0
KEL	19	0.1		20	0.1		17	0.1		1.0
THALF	19	8.2		20	8		17	9.6		1.0

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

1. The desacetyldiltiazem mean plasma levels peaked at 14 and 20 hours for the test and reference products, respectively, under nonfasting conditions and at 24 hours for the test product under fasting conditions.

2. For Mylan's test product, the mean AUCT, AUCI and Cmax values were 4.6%, 8.5% and 3.5% higher, respectively, than the reference product values under nonfasting conditions. The mean AUCT, AUCI and Cmax values under fasting conditions are lower than under nonfasting conditions.

3. The ratios of the test to the reference arithmetic mean are within the acceptable range of 0.8-1.2 for AUCT, AUCI and Cmax.

Table XII

Mean Plasma desmethyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240mg Diltiazem HCl XR Capsule under Fasting and Nonfasting Conditions

	Treatment A Mylan-Test Nonfasting			Treatment B Reference Nonfasting			Treatment C Mylan-Test Fasting			Ratio
Time (h)	N	Mean ng/ml	CV	N	Mean ng/ml	CV	N	Mean ng/ml	CV	A/B
0	19	0	.	20	0	.	20	0	.	
1	20	0	.	19	0	.	20	2.5	79.5	
2	20	2.2	98.6	19	3.5	93.8	20	8.2	39.2	0.6
3	19	10.1	51.9	20	10.7	46.2	20	11.6	42.5	0.9
4	19	14.4	40.1	20	13.2	42.5	19	11.9	35.1	1.1
5	19	18	35.5	19	15.9	38.9	20	12.3	42.2	1.1
6	20	25.8	30.2	20	21.7	36.1	20	12.5	45.5	1.2
7	19	26.9	30.3	20	24.6	30.6	20	13.7	41.5	1.1
8	19	27.4	29.2	20	24.6	32.1	19	12.7	39.3	1.1
10	20	25.9	27.7	20	26.6	25.8	20	13.4	39	1.0
12	20	24.9	26.8	19	26.8	34.9	20	13.6	37.4	0.9
14	20	23.1	26.9	19	25	36	20	13.3	39	0.9
16	20	21.3	20.1	19	23	32.1	20	13.5	40.3	0.9
20	20	16.6	20.5	20	19.4	29.8	20	11.7	41	0.9
24	19	13.8	23.4	20	16	30.3	20	10.6	40.3	0.9
30	20	9.7	27.8	19	10.8	35.5	20	8.4	49.6	0.9
36	20	5.3	42.7	20	5.8	39.9	19	5	72.2	0.9
48	20	0.7	189.1	19	0.9	135.8	19	1.8	121.7	0.8

	A			B			C			Ratio (A/B)
AUCT	20	576.4	19.8	20	614.1	25.9	20	411.3	35.3	0.9
AUCI	20	633.4	18.9	20	662	23.5	20	467.8	34.4	1.0
CMAX	20	30.1	24.8	20	31.2	26	20	16.2	31.4	1.0
TMAX	20	9.1		20	9.4		20	12		1.0
KEL	20	0.1		20	0.1		20	0.1		1.0
THALF	20	8.5		20	7.6		20	9.6		1.1

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Kel=h^{-1}, Half-life= h^{-1}

1. The desmethyldiltiazem mean plasma levels peaked at 8 and 12 hours for the test and reference products, respectively, under nonfasting conditions and at 7 hours for the test product under fasting conditions.

2. For Mylan's test product, the mean AUCT, AUCI and Cmax values were lower by 6.1%, 4.3% and 3.5%, respectively, than the reference product values under nonfasting conditions. The mean AUCT, AUCI and Cmax values under fasting conditions are lower than under nonfasting conditions.

3. The ratios of the test arithmetic mean to the reference arithmetic mean are within the acceptable range of 0.8-1.2 for AUCT, AUCI and Cmax.

IX. Formulations:

Mylan's formulations for its Diltiazem HCl XR 240 mg, 180 mg and 120 mg Capsules are shown in Table XIII (attachment).

X. In vitro Dissolution Testing: Please see Table XIV(attachment)
USP Drug Release Test 2, suppl. 5, pp 3409-10.

Method: USP 23 apparatus II (paddle) at 100 rpm
Media: Water, 900 ml @ 37°C ± 0.5°C
Number of Capsules: 12
USP Drug Release Test 2
Note the firm has requested USP to change specifications for 10 hour period from "between 70% and 90%" to "between

Limits:
1 hour between
4 hour between
10 hour between
15 hour NLT

Test Product: Mylan's Diltiazem HCl XR Capsule 240 mg, Lot #2C004H
180 mg, Lot #2D002A
120 mg, Lot #2D001A

Reference Product: Rhone-Poulenc's Dilacor^{R} XR Capsule
240 mg, Lot #N54506
180 mg, Lot #N27610
120 mg, Lot #P14610

The dissolution testing results are presented in table XI. The USP specifications are met in all cases except for 10 hour 180 mg and 240 mg Test products and 240 mg Reference product. The firm has therefore requested USP to change specifications for the 10 hour period.

XI. Comments:

1. The firm's single-dose bioequivalence study #Dilt9631 under fasting conditions, conducted on its 240 mg Diltiazem HCl XR Capsule is acceptable. The 90% confidence intervals for lnAUC(0-24) and lnCmax are within the acceptable range of 80-125% for Diltiazem, Desmethyldiltiazem and Desacetyldiltiazem. Subject #22 was excluded from statistical analysis. Subject 22's pharmacokinetic parameters for diltiazem and desacetyldiltiazem in the repeat confirmatory study (9631A) are similar to the original study data and therefore his original study data were excluded from statistical analysis as being aberrant.

2. The firm's multiple-dose bioequivalence study #Dilt9633 under fasting conditions, conducted on its 240 mg Diltiazem HCl XR Capsule is acceptable. The 90% confidence intervals for lnAUC(0-24) and lnCmax are within the acceptable range of 80-125% for Diltiazem, Desmethyldiltiazem and Desacetyldiltiazem. Each subject attained steady-state.

3. The firm's single-dose bioequivalence study #Dilt9632 under fasting and nonfasting conditions, conducted on its 240 mg Diltiazem HCl XR Capsule is acceptable. The ratios of the test to the reference arithmetic mean are within 0.80-1.20 for Diltiazem, Desmethyldiltiazem and Desacetyldiltiazem under nonfasting conditions.

4. The formulations for Diltiazem HCl XR Capsule, 120 mg and 180 mg are proportionally similar to the 240 mg strength of the test product. Waivers of the in vivo bioequivalence study requirements for the firm's Diltiazem HCl Extended Release (XR), 180 mg and 120 mg Capsules may be granted.

5. The firm conducted dissolution testing on its Diltiazem HCl XR Capsules, 120 mg, 180 mg and 240 mg in water as per USP 23, supplement #5, Test #2, page 3409-10. The test products do meet USP specifications for Test #2 in water at all time points. Note: the firm has requested USP to change specification for the 10 hour time point.

XII. Deficiency Comment: None

XIII. Recommendations:

1. The single-dose bioequivalence study #Dilt9631, conducted by Mylan Pharmaceuticals, Inc., on its Diltiazem HCl Extended Release (XR) 240 mg Capsule, lot #2C004H, comparing it to Dilacor XR® 240 mg Capsule, lot #N54506 manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Diltiazem HCl XR Capsule, 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR® 240 mg Capsule.

2. The multiple-dose steady-state bioequivalence study #Dilt9633, conducted by Mylan Pharmaceuticals, Inc., on its Diltiazem HCl Extended Release (XR) 240 mg Capsule, lot #2C004H, comparing it to Dilacor XR® 240 mg Capsule, lot #N54506, manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Diltiazem HCl XR, Capsule 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR® 240 mg Capsule.

3. The single-dose post-prandial bioequivalence study #Dilt9632, conducted by Mylan Pharmaceuticals, Inc., on its Diltiazem HCl

Extended Release (XR) 240 mg Capsule, lot #2C004H , comparing it to Dilacor XR® 240 mg Capsule manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Diltiazem HCl XR, Capsule 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR® 240 mg Capsule.

4. The dissolution testing conducting by Mylan Pharmaceuticals, Inc., on its Diltiazem HCl Extended Release (XR), 240 mg, 180 mg and 120 mg Capsules, lot #2C004H ,#2D002A and #2D001A, respectively, has been found acceptable by the Division of Bioequivalence.

The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP 23 Apparatus 2 (Paddle) at 100 rpm. The test product should meet the following specifications:

USP Drug Release Interim specifications.
Note the firm has requested USP to change limits for 10 hour period from "between 70% and 90%" to

Limits:
1 hour between
4 hour between
10 hour between
15 hour NLT

5. Waivers of the in vivo bioequivalence study requirements for the firm's Diltiazem HCl Extended Release (XR), 180 mg and 120 mg Capsules are granted.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-124 APPLICANT:Mylan, Inc.

DRUG PRODUCT:Diltiazem HCl XR Capsules 120mg, 180mg and 240mg

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 USP 23 with drug release interim specifications:

Limits: 1 hour between
4 hour between
10 hour between
15 hour NLT

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,

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

CC: ANDA 75-124
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-658/ A.P.Patel

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Printed in final on 2/5/98

2/5/98

A.P.Patel
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Acting Team Leader,
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Date: 2/4/98

Concur:
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Date: 2/5/98

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF) — Strengths: 240mg
   Outcome: AC

2. **FOOD STUDY** (STP) — Strengths: 240mg
   Outcome: AC

3. **MULTIPLE DOSE STUDY** (STM) — Strengths: 240mg
   Outcome: AC

4. **DISSOLUTION DATA** (DIS) — All Strengths
   Outcome: **AC**

5. **WAIVER** (WAI) — Strengths: 120mg and 180mg
   Outcome: AC

Outcome: AC

Outcome Decisions:

AC - Acceptable
UN - Unacceptable (fatal flaw)
NC - No Action
IC - Incomplete

WINBIO COMMENTS:Biostudies and dissolution tests acceptable