CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-138

BIOEQUIVALENCE

Verapamil HCl ER Capsules
120 mg, 180 mg and 240 mg
ANDA #75-138
Reviewer: Moheb H. Makary
WP 75138SDW.598

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
May 27, 1998

Review of an Amendment

I. Objective:

The firm has replied to the reviewer's comment made in the review of the May 29, 1997 submission (bioequivalence studies on Verapamil HCl ER Capsules, 240 mg and dissolution data). The firm was advised to submit a sprinkling bioequivalence study on its test product.

In this amendment the firm submitted the results of a sprinkling bioequivalence study on its Verapamil HCl ER Capsules, 240 mg. In addition, the firm requested waivers of *in vivo* bioequivalence study requirements for its 120 mg and 180 mg strengths.

II. Background:

In the original application (May 29, 1997 submission), the firm had submitted three acceptable bioequivalence studies on its Verapamil HCl ER Capsules, 240 mg and dissolution data.

III. Study #VERA-9784 For Single-Dose, Two-Way Crossover On Verapamil HCl Extended Release Capsules, 240 mg, Administered over Tablespoon of Applesauce:

Objective: The objective of the study was to investigate the bioequivalence of Mylan's Verapamil HCl ER capsules to Verelan^{R} SR capsules under fasting conditions following a single, oral 240 mg (1x240 mg) dose sprinkled in one tablespoon of applesauce.

Clinical site:	Drug Study Unit, Clinical and Pharmacologic Research, Morgantown, WV
Analytical site:	
Investigators:	Thomas S. Clark, M.D. Principal Investigator
Study design:	Open-label, randomized, single-dose, two-way crossover sprinkled bioequivalence study.

Dosing date:	January 30, 1998 - Period I February 13, 1998 - Period II
Analytical date:	March 24, 1998 - April 21, 1998
Subjects:	Thirty-eight (38) male subjects were enrolled and successfully completed the study. The clinic portion of the study was conducted in one group.
Selection criteria:	The subjects were between 18 to 55 years of age. All subjects were within ±10% of their ideal body weight for height and body frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983. Subjects were judged to be in good health following a complete physical examination, EKG and medical history within fourteen days of the start of the study. In addition, urine samples at the time of the medical examination were free of drug abuse (including marijuana). Good health was confirmed by normal findings in the following tests: biochemical profile, hematology and urinalysis.
Exclusion criteria:	Consisted of adverse reactions or allergy to verapamil or any other calcium channel blockers, history of alcohol or drug abuse, history of cardiovascular, neurological, neuropsychiatric, gastrointestinal, hepatic, renal, hematological and/or respiratory diseases.
Restrictions:	Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. In addition, no concomitant medication is permitted during the study period. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine-containing products for 48 hours prior to, and during the course of the study.
Dose and Treatments:	After a supervised overnight fast (at least 10 hours) subjects received an oral dose of the assigned formulation sprinkled on one

tablespoon of applesauce with 240 mL of water.
Treatment A: 1x240 mg Verelan®SR capsule (Lederle), lot #446-298, Exp. 3/99, potency 101.0%, content uniformity 97.4% (%CV=1.5).

Treatment B: 1x240 mg Verapamil HCl ER Capsule (Mylan), lot #2C004J, batch size potency 100.0%, content uniformity 101.5% (%CV=1.8).

Washout period: Two weeks

Food and fluid intake: Subjects fasted for ten hours prior to dosing. Lunch was served five hours after dosing. Dinner was served ten hours after dosing. Water was not allowed from two hours before until two hours after dosing, except for the dosing water (240 mL).

Blood samples: Ten mL (10) blood samples were collected at 0 (pre-dose) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, and 48 hours after dosing. Plasma samples were immediately frozen.

Subject welfare: Vital signs (blood pressure, pulse rate and Lead II ECG) were measured pre-dose and prior blood collection at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36 and 48 hours.

Assay Methodology:

Determination of Verapamil and Norverapamil plasma concentrations were performed by internal standard.

Sensitivity: The limit of quantitation was 2.5 ng/mL for Verapamil and Norverapamil.

Linearity: The assay was linear over the concentration range of 2.5 to 400.0 ng/mL for both Verapamil and Norverapamil.

Assay specificity: Blank plasma samples from subjects in the study indicated that there were no

interferences with Verapamil, Norverapamil or the internal standard. Additionally, the following compounds were chromatographed and did not interfere with either analyte or the internal standard: acetaminophen, aspirin, ibuprofen, citrate phosphate dextrose adenine, caffeine, heparin-sodium and nicotine.

Recovery: The recovery is 80.7% for Verapamil and is 77.1% for Norverapamil.

Interday precision: Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from 3.75% to 4.97% for Verapamil and ranged from 4.2% to 5.2% for Norverapamil.

Intraday precision: Intraday precision were calculated using six spiked samples at each of three concentrations 25, 100 and 250 ng/mL assayed on the same day. The coefficients of variation ranged from 1.12% to 1.29% for Verapamil and from 1.09% to 1.91% for Norverapamil.

Stability: Freeze-Thaw Stability: Verapamil and Norverapamil were spiked into plasma at low and high concentrations. These samples were subjected to three freeze-thaw cycles. Verapamil and Norverapamil samples were found to be stable through three freeze/thaw cycles. Processed sample stability: processed (extracted) and reconstituted samples were set at room temperature up to 96 hours. The samples did not show significant degradation when stored at room temperature up to 96 hours.
Long term stability: stability was assessed by quantitation of spiked plasma samples which were frozen (-70°C) prior to initiation of the fasted study. The spiked samples contained approximately 250 ng/mL and 2.5 ng/mL Verapamil and Norverapamil. The results showed no degradation of Verapamil or Norverapamil for a period up to 184 days.

Statistical Analysis:

Statistical analysis was performed on Verapamil and Norverapamil data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetics parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval.

IV. In Vivo Results:

Thirty-eight (38) normal, healthy subjects were recruited and successfully completed both phases of the clinical portion of the study. There were 13 adverse events (10 subjects) reported for this study. All were reported as probably or possibly drug related. There were no serious or life threatening adverse events reported for this study.

The plasma concentrations and pharmacokinetics parameters for Verapamil and Norverapamil are summarized in Tables I and II.

Table I

Mean Plasma Verapamil Concentrations and Pharmacokinetics Parameters Following an Oral Dose of 240 Verapamil HCl ER (1x240 mg Capsule) Sprinkled over One Tablespoon of Applesauce
(N=38)

Time hr	Treatment A Reference Lot #446-298 ng/mL(CV)	Treatment B Mylan-Test Lot #2C004J ng/mL(CV)
0	0	0
1	13.60 (58.2)	13.89 (60.4)
2	13.97 (57.2)	12.13 (52.9)
3	16.34 (56.7)	13.44 (50.9)
4	20.19 (53.5)	16.91 (49.6)
5	26.26 (49.6)	22.47 (51.7)
6	45.38 (48.0)	46.56 (55.5)
7	48.47 (46.4)	53.84 (51.5)
8	51.47 (48.9)	55.43 (50.8)
9	52.19 (51.2)	55.92 (55.4)
10	52.47 (48.0)	54.41 (53.7)

11	55.34 (44.4)	58.86 (49.7)
12	50.98 (41.9)	54.22 (43.0)
14	46.48 (39.1)	47.52 (41.7)
16	38.92 (39.3)	39.12 (38.7)
24	27.84 (45.4)	27.70 (43.6)
36	10.58 (60.1)	10.51 (65.3)
48	4.67 (91.9)	4.26 (104)

			B/A	90% CI
AUC(0-t) (ng.hr/mL)	1180.94 (42.6)	1195.58 (44.6)	1.02	
AUCINf (ng.hr/mL)	1284.41 (42.6)	1280.81 (45.8)	0.99	
Cpeak(ng/mL)	61.19 (45.0)	66.34 (48.8)	1.08	
Tpeak (hr)	9.94	9.18		
Kel(1/hr)	0.072	0.077		
T1/2(hr)	10.19	9.43		

LnAUC(0-t)	95-110%
LnAUCI	93-108%
LnCpeak	99-119%

1. For Verapamil, mean values for AUC(0-t), Cpeak and AUCinf were 1.2%, 6.6% and 0.28% higher and lower, respectively, for the test product than for the reference product. The differences are not statistically significant and 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 similar to those submitted by the firm.

2. The Verapamil plasma levels peaked at 11 hours for both the test and the reference products, following their administration under sprinkling conditions.

3. Systolic and diastolic blood pressure, heart rate and percent change from baseline of the ECG PR interval were analyzed for statistical differences. There were no clinically significant differences in the parameters evaluated.

Table II

Mean Plasma Norverapamil Concentrations and Pharmacokinetics Parameters Following an Oral Dose of 240 Verapamil HCl ER (1x240 mg Capsule) Sprinkled over One Tablespoon of Applesauce

(N=38)

Time hr	Treatment A Reference Lot #446-298 ng/mL(CV)	Treatment B Mylan-Test Lot #2C004J ng/mL(CV)
0	0	0
1	9.74 (47.7)	10.28 (46.4)
2	13.00 (32.4)	11.97 (28.8)
3	17.00 (35.3)	14.23 (30.4)
4	20.23 (35.1)	17.17 (30.5)
5	25.05 (33.0)	21.31 (31.1)
6	35.29 (27.7)	32.26 (31.0)
7	39.76 (27.2)	39.86 (32.6)
8	43.36 (30.0)	44.08 (32.4)
9	45.96 (31.5)	46.56 (35.7)
10	47.88 (31.6)	48.45 (39.1)
11	50.05 (30.1)	51.79 (35.4)
12	49.42 (29.5)	52.14 (33.7)
14	48.42 (26.6)	50.08 (33.2)
16	44.71 (30.2)	45.75 (32.2)
24	35.65 (28.9)	36.66 (33.0)
36	18.19 (39.5)	18.69 (41.7)
48	9.02 (52.9)	8.66 (57.1)

			B/A	90% CI
AUC(0-t) (ng.hr/mL)	1368.75 (27.6)	1387.86 (31.5)	1.01	
AUCINf (ng.hr/mL)	1554.58 (30.9)	1548.04 (34.7)	1.00	
Cpeak(ng/mL)	52.81 (28.3)	55.35 (34.2)	1.05	
Tpeak (hr)	11.47	11.32		
Kel(1/hr)	0.061	0.063		
T1/2(hr)	12.17	11.60		
LnAUC(0-t)				95-106%
LnAUCI				94-105%
LnCpeak				97-110%

1. For Norverapamil, mean values for AUC(0-t), Cpeak and AUCinf were 1.3%, 4.8% and 0.42% higher and lower, respectively, for the test product than for the reference product. The differences are not statistically significant and 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 similar to those submitted by the firm.

2. The Norverapamil plasma levels peaked at 11 and 12 hours for the reference and the test products, respectively, following their administration under sprinkling conditions.

V. Comments:

1. The firm's single-dose sprinkling bioequivalence study #VERA-9784, conducted on its 240 mg Verapamil HCl ER capsule is acceptable. The two study drugs did not differ significantly with respect to mean values for any of the pharmacokinetics parameters. The ratios of the test mean to the reference mean for AUC(0-t), AUCinf and Cpeak are within the acceptable range of 0.8-1.2 for Verapamil and Norverapamil under sprinkling conditions. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCpeak are within the acceptable range of 80-125% for Verapamil and Norverapamil.

2. The firm had previously submitted three acceptable bioequivalence studies on its Verapamil HCl ER Capsules, 240 mg and dissolution data (submission dated May 29, 1997).

3. Mylan's Verapamil HCl ER Capsules, 120 mg and 180 mg are proportionally similar to its 240 mg strength. Comparative compositions are attached.

4. The in vitro dissolution testing for the test products 120 mg, 180 mg and 240 mg Verapamil HCl ER capsules is acceptable. Comparative dissolution testing is attached.

5. It should be noted that the Mylan's lot #2C004J used in the sprinkling study is the same as that used to conduct the fasting (VERA-9669), post-prandial (VERA-9612) and steady-state (VERA-9674) bioequivalence studies submitted in the original application. However, the reference product, Lederle's lot #446-298, used in the sprinkling bioequivalence study is different from that used in the original fasting, post-prandial and steady-state bioequivalence studies due to the expiration of the original lot prior to the initiation of the sprinkling study.

VI. Recommendations:

1. The single-dose sprinkling bioequivalence study #VERA-9784, conducted by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended-Release 240 mg Capsule, lot #2C004J, comparing it to Verelan^{R} SR 240 mg Capsule manufactured by Lederle, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Verapamil HCl Extended-Release 240 mg Capsule, is bioequivalent to Lederle's Verelan^{R} SR Capsule, 240 mg under sprinkling conditions.

2. The dissolution testing conducting by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended-Release 240 mg, 180 mg and 120 mg Capsules, lot #2C004J, 2D002J and 2D001J, respectively, is acceptable. The formulations for Verapamil HCl Extended-Release 180 mg and 120 mg strengths are proportionally similar to the 240 mg strength which underwent acceptable bioequivalence testing. Waivers of in vivo bioequivalence study requirements for the 180 mg and 120 mg Capsules of the test product are granted. The Division of Bioequivalence deems Verapamil HCl Extended-Release Capsules, 180 mg and 120 mg, manufactured by Mylan Pharmaceuticals Inc., to be bioequivalent to Verelan^{R} SR Capsules, 180 mg and 120 mg, respectively, manufactured by Lederle.

3. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 100 rpm. Based on the submitted data the following tentative specifications are recommended:

2	hours
4	hours
8	hours
24	hours

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT BMD 9/3/98
FT INITIALLED BDAVIT Barbara M Davit Date: 9/4/98

Concur: Dale P. Conner Date: 9/19/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/9-2-98, 9-4-98, 75138SDW.598
cc:

Verapamil HCl ER Capsules
120 mg, 180 mg and 240 mg
ANDA #75-138
Reviewer: Moheb H. Makary
WP 75138D.D97

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
December 31, 1997

Review of an Amendment

I. Objective:

The firm submitted this amendment to its ANDA #75-138 for Verapamil HCl ER Capsules, 240 mg provides for the inclusion of two additional dosage strengths (120 mg and 180 mg). All three strengths are compositionally proportional as they consist of a combination of three beads, Verapamil HCl Immediate Release Beads, (635 mg/gm); Verapamil HCl Extended-release Beads, (534.4 mg/gm); Verapamil HCl Extended-release Beads, (587.4 mg/gm); and Talc. A specific amount of the aforementioned beads is weighed for use in encapsulation based on the potency of the beads and strength of the capsule. The formulations of the three strengths are shown in Table I. Comparative *in vitro* dissolution data for Mylan's Verapamil HCl ER Capsules, 120 mg, 180 mg and 240 mg versus Lederle's Verelan^{R} Capsules, 120 mg, 180 mg and 240 mg were also submitted Table II. The firm requested waivers of *in vivo* bioequivalece study requirements for the 120 mg and 180 mg dosage strengths.

II. Background:

The firm had previously submitted three bioequivalence studies on its Verapamil HCl ER Capsules, 240 mg. The studies were provided in the original ANDA for the 240 mg product which was submitted May 28, 1997. The ANDA has been found incomplete since the firm was advised to submit additional sprinkling bioequivalence study on its Verapamil HCl ER Capsules, 240 mg (review dated November 20, 1997).

III. Recommendation:

Waivers of *in vivo* bioequivalece study requirements for the firm's Verapamil HCl ER Capsules, 120 mg and 180 mg can not be granted since the ANDA for Verapamil HCl ER Capsules, is incomplete. The firm is advised to resubmit the waiver request upon submitting a sprinkling bioequivalence study on its Verapamil HCl ER Capsules, 240 mg.

The firm should be informed of the above recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

Date: 4/29/98

RD INITIALLED SNERURKAR
FT INITIALLED SNERURKAR Date: 4/29/1998

Concur: Dale P. Conner Date: 4/30/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/4-20-98, 4-29-98, 75138D.D97
cc:

Verapamil HCl ER Capsules
240 mg
ANDA #75-138
Reviewer: Moheb H. Makary
WP 75138SD.597

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
May 29, 1997

Review of Bioequivalence Studies and Dissolution Data

I. Objective:

The firm submitted the data and results from three (3) *In Vivo* Bioequivalence Studies, and the *In Vitro* dissolution data for its Verapamil HCl Extended Release Capsules, USP, 240 mg.

The three *in vivo* bioequivalence studies titled:

1. Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Mylan and Lederle (Verelan® SR) 240 mg Verapamil HCl Sustained-Release Capsules in Healthy Adult Males Under Fasting Conditions - Protocol No. VERA-9669.

2. Comparative, Randomized, Single-Dose, 3-Way Crossover Bioavailability Study of Mylan and Lederle (Verelan® SR) 240 mg Verapamil HCl Sustained-Release Capsules in Healthy Adult Males Under Nonfasting and Fasting Conditions - Protocol No. VERA-9612

3. Comparative, Randomized, Steady-State, 2-Way Crossover Bioavailability Study of Mylan and Lederle (Verelan® SR) 240 mg Verapamil HCl Sustained-Release Capsules in Healthy Adult Males Under Fasting Conditions - Protocol No. VERA-9674

II. Background:

Verapamil is a calcium-channel blocking agent. Verapamil HCl is almost a white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform and methanol. Its mechanism of action involves inhibition of ATP-dependent calcium transport properties of the sarcolemma and intrinsic calcium-sensitive ATPase. The drug is well absorbed orally (over 90%). However, extensive first-pass metabolism

reduces absolute bioavailability to approximately 20%. An N-dealkylated metabolite, norverapamil, is active and upon single dose administration the AUC of this metabolite equals or exceeds that of the parent drug. The mean elimination half-life for verapamil in single dose studies ranged from 2.8 to 7.4 hours. As an anti-anginal agent, the usual dose is 80-120 mg three times daily. As an anti-arrhythmic, the usual dose ranges from 240-320 mg or from 240-480 mg per day (in 3 or 4 divided doses). To treat essential hypertension, the usual initial dose for monotherapy is 80 mg three times daily, individualized to 360 mg daily.

Verapamil HCl is marketed as 80 and 120 mg conventional release tablets. The drug is also marketed as a 120 mg, 180 mg and 240 mg sustained release tablets and capsules for treatment of essential hypertension. The usual daily dose is 240 mg once daily in the morning. Labeling describes higher doses if necessary. Labeling also indicates that the drug should be dosed with food for the tablets but not for the capsules.

III. Study #VERA-9669 For Single-Dose, Two-Way Crossover On Verapamil HCl Extended Release Capsules, 240 mg, Under Fasting Conditions:

Objective: The objective of the study was to compare the bioavailability of verapamil-ER capsules manufactured by Mylan Pharmaceuticals Inc., with that of Lederle product (Verelan^{R} SR), following an oral administration of a single 240 mg dose (1x240 mg capsule) of each product under fasting conditions.

Clinical site: Drug Study Unit, Clinical and Pharmacologic Research, Morgantown, WV

Analytical site:

Investigators: Thomas S. Clark, M.D.
Principal Investigator

Study design: Single-dose, two-way crossover bioequivalence study, under fasting conditions.

Subjects: Forty-seven (47) male subjects were accepted for entry into the clinical portion of the

study. Forty-six (46) subjects successfully completed both phases of the clinical portion of the study. The clinic portion of the study was conducted in three groups. Group A consisted of volunteers 1-12, Group B consisted of volunteers 12-25 and Group C consisted of volunteers 26-47. The dosing dates for this study were as following:

	Phase I	Phase II
Group A	October 15	October 29, 1996
Group B	October 27	November 10, 1996
Group C	November 8	November 22, 1996

Selection criteria: The subjects were between 19 to 55 years of age. All subjects were within ±10% of their ideal body weight for height and body frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983. Subjects were judged to be in good health following a complete physical examination, EKG and medical history within fourteen days of the start of the study. In addition, urine samples at the time of the medical examination were free of drug abuse (including marijuana). Good health was confirmed by normal findings in the following tests: biochemical profile, hematology and urinalysis.

Exclusion criteria: Consisted of adverse reactions or allergy to verapamil or any other calcium channel blockers, history of alcohol or drug abuse, history of cardiovascular, neurological, neuropsychiatric, gastrointestinal, hepatic, renal, hematological and/or respiratory diseases.

Restrictions: Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. In

addition, no concomitant medication is permitted during the study period. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine-containing products for 48 hours prior to, and during the course of the study.

Dose and Treatments:

Treatment A: 1x240 mg Verelan®SR capsule (Lederle), lot #428-233, Exp. 4/97, potency 98.5%, content uniformity 98.0% (CV=1.5%), administered following an overnight fast.

Treatment B: 1x240 mg verapamil HCl ER Capsule (Mylan), lot #2C004J, batch size Capsules, potency 100.0%, content uniformity 101.5% (CV=1.8%), administered following an overnight fast.

Washout period: Two weeks

Food and fluid intake: Subjects fasted for ten hours prior to dosing. Lunch was served five hours after dosing. Dinner was served ten hours after dosing. Water was not allowed from two hours before and until two hours after dosing, except for the dosing water (240 mL).

Blood samples: Ten mL (10) blood samples were collected at 0 (pre-dose) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, and 48 hours after dosing. Plasma samples were immediately frozen.

Subject welfare: Vital signs (blood pressure, pulse rate and Lead II ECG) were measured pre-dose and prior blood collection at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36 and 48 hours.

Assay Methodology:

Sensitivity: The limit of quantitation was 2.5 ng/mL for verapamil and norverapamil.

Linearity: The assay was linear over the concentration range of 2.5 to 400.0 ng/mL for both verapamil and norverapamil.

Assay specificity: Blank plasma samples from subjects in the study indicated that there were no interferences with verapamil, norverapamil or the internal standard. Additionally, the following compounds were chromatograms and did not interfere with either analyte or the internal standard: acetaminophen, aspirin, ibuprofen, anti-coagulant (citrate phosphate dextrose adenine), caffeine, heparin-sodium and nicotine.

Recovery: The recovery is 80.7% for verapamil and is 77.1% for norverapamil.

Interday precision: Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from 3.75% to 4.97% for verapamil and ranged from 4.2% to 5.2% for norverapamil.

Intraday precision: Intraday precision were calculated using six spiked samples at each of three concentrations 25, 100 and 250 ng/mL assayed on the same day. The coefficients of variation ranged from 1.12% to 1.29% for verapamil and from 1.09% to 1.91% for norverapamil.

Stability: Freeze-Thaw Stability: Verapamil and norverapamil were spiked into plasma at low and high concentrations. These samples were

subjected to three freeze-thaw cycles. Verapamil and norverapamil samples were found to be stable through three freeze/thaw cycles. Processed sample stability: processed (extracted) and reconstituted samples were set at room temperature up to 96 hours. The samples did not show significant degradation when stored at room temperature up to 96 hours. Long term stability: stability was assessed by quantitation of spiked plasma samples which were frozen prior to initiation of the fasted study. The spiked samples contained approximately 250 ng/mL and 25 ng/mL verapamil and norverapamil. The results showed no degradation of verapamil or norverapamil for a period up to 184 days.

Statistical Analysis:

Statistical analysis was performed on verapamil and norverapamil data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetics parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval. The subjects in the study were dosed in three separate groups. An analysis of variance was performed to assess the group effect and determine the poolability of the three groups. A mode with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, treatments and periods was performed. No statistically significant group effects were observed for the pharmacokinetics parameters by using the above model. The firm dropped the group effect, and the standard two way crossover model was employed.

IV. In Vivo Results:

Forty-seven (47) normal, healthy subjects were recruited for the study and forty-six (46) successfully completed both phases of the clinical portion of the study. Subject #4 withdrew from the study due to personal reasons that were not study related. Five adverse events (headache) were reported in four subjects dosed over the course of the study that were probably drug related. No subjects withdrew or were withdrawn due to adverse

events. There were no serious or life-threatening adverse events reported for this study.

The plasma concentrations and pharmacokinetics parameters for verapamil and norverapamil are summarized in Tables I and II.

Table I

Mean Plasma Verapamil Concentrations and Pharmacokinetics Parameters Following an Oral Dose of 240 Verapamil HCl ER (1x240 mg Capsule) under Fasting Conditions
(N=46)

Time hr	Treatment A Reference Lot #428-233 ng/mL(CV)	Treatment B Mylan-Test Lot #2C004J ng/mL(CV)
0	0	0
1	10.55 (82.0)	9.96 (72.6)
2	10.90 (67.8)	9.87 (67.9)
3	12.96 (80.5)	12.21 (78.1)
4	17.52 (65.8)	14.78 (74.2)
5	23.40 (61.2)	19.28 (71.9)
6	41.70 (52.0)	38.92 (56.7)
7	43.36 (47.9)	43.97 (48.6)
8	47.60 (55.0)	47.51 (53.7)
9	46.40 (50.4)	47.74 (53.2)
10	43.98 (47.6)	47.50 (47.5)
11	46.47 (43.8)	49.49 (41.3)
12	41.97 (44.6)	45.76 (44.3)
14	34.77 (42.7)	36.78 (45.9)
16	28.99 (43.2)	30.27 (47.8)
24	21.32 (50.3)	22.98 (51.3)
36	7.65 (67.8)	8.84 (74.0)
48	2.71 (119)	3.17 (121)

90% CI

AUC(0-t) (ng.hr/mL)	926.40 (46.9)	975.76 (47.7)
AUCINf (ng.hr/mL)	1005.24 (44.3)	1064.36 (45.8)
Cpeak(ng/mL)	55.04 (47.9)	58.66 (44.7)
Tpeak (hr)	9.02	9.15
Kel(1/hr)	0.078	0.075
T1/2(hr)	9.74	10.10

LnAUC(0-t)	98-112%
LnAUCI	100-111%
LnCpeak	99-116%

1. For verapamil, the least squares means for AUC(0-t), AUCI and Cpeak values were 5.2%, 5.9% and 6.6% higher, respectively, for the test product than for the reference product. The differences are not statistically significant and 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 similar to those submitted by the firm.

2. The verapamil plasma levels peaked at 8 and 11 hours for the reference and the test products, respectively, following their administration under fasting conditions.

3. Systolic and diastolic blood pressure, heart rate and percent change from baseline of the ECG PR interval were analyzed for statistical differences. There were no clinically significant differences in the parameters evaluated.

4. Additional analysis of variance was performed by the reviewer. The following model

Y = SEQ SUBJ(SEQ) PER(group) TRT;

was employed in the statistical analysis of the study. The following 90% confidence intervals for LnAUC(0-t), LnAUCI and LnCpeak were obtained:

Verapamil

LnAUC(0-t)	98.1-112.1%
LnAUCI	99.9-111.2%
LnCpeak	99.3-116.7%

The 90% confidence intervals for the above pharmacokinetics parameters calculated using the above model remained within the acceptable range of 80-125%.

Table II

Mean Plasma Norverapamil Concentrations and Pharmacokinetics Parameters Following an Oral Dose of 240 Verapamil HCl ER (1x240 mg Capsule) under Fasting Conditions

(N=46)

Time hr	Treatment A Reference Lot #428-233 ng/mL(CV)	Treatment B Mylan-Test Lot #2C004J ng/mL(CV)
0	0	0
1	8.28 (62.3)	7.82 (58.5)
2	11.65 (39.0)	10.59 (34.7)
3	14.23 (40.2)	13.38 (42.5)
4	18.39 (37.3)	16.24 (43.3)
5	23.23 (37.3)	20.06 (42.4)
6	33.62 (33.3)	30.86 (38.0)
7	37.14 (30.5)	36.14 (36.1)
8	41.69 (34.9)	39.94 (36.3)
9	43.20 (33.7)	42.12 (36.8)
10	43.88 (34.5)	44.14 (34.3)
11	45.53 (31.2)	44.94 (29.6)
12	43.91 (32.4)	44.61 (31.4)
14	41.02 (29.9)	41.64 (31.8)
16	37.36 (31.1)	37.48 (32.2)
24	30.28 (34.7)	31.50 (36.1)

36	15.69 (43.2)	16.79 (48.4)
48	7.04 (59.6)	7.70 (67.9)

			90% CI
AUC(0-t) (ng.hr/mL)	1184.99 (31.3)	1204.80 (31.7)	
AUCINf (ng.hr/mL)	1329.03 (33.2)	1365.16 (36.2)	
Cpeak(ng/mL)	48.19 (31.3)	49.15 (31.3)	
Tpeak (hr)	10.9	10.9	
Kel(1/hr)	0.064	0.063	
T1/2(hr)	11.9	11.9	
LnAUC(0-t)			97-106%
LnAUCI			98-106%
LnCpeak			96-107%

1. For norverapamil, the least squares means for AUC(0-t), AUCI and Cpeak values were 1.7%, 2.7% and 2.0% higher, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of for log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

2. The norverapamil plasma levels peaked at 11 hours for both the test and the reference products following their administration under fasting conditions.

3. Additional analysis of variance was performed by the reviewer. The following model

Y = SEQ SUBJ(SEQ) PER(group) TRT;

was employed in the statistical analysis of the study. The following 90% confidence intervals for LnAUC(0-t), LnAUCI and LnCpeak were obtained:

Norverapamil

LnAUC(0-t)	97.3-106.0%
LnAUCI	98.2-106.2%

LnCpeak 96.4-107.7%

The 90% confidence intervals for the above pharmacokinetics parameters calculated using the above model remained within the acceptable range of

V. Study #VERA-9612 For Post-Prandial, Single-Dose Bioequivalence Study, Three-way Crossover on Verapamil HCl ER Capsules, 240 mg

The objective of this study was to evaluate the effect of food on the rate and extent of absorption of Mylan's verapamil HCl ER 240 mg capsule relative to Verelan^{R} SR 240 mg capsule (Lederle), following administration of a 240 mg dose (1 capsule).

Clinical site: Drug Study Unit, Clinical and Pharmacologic Research, Morgantown, WV

Analytical site:

Study date: Clinical phase: November 16 - December 14, 1996
Analytical phase: January 30-February 21, 1997

Investigators: Thomas S. Clark, M.D.
Principal Investigator
Mylan Pharmaceuticals Inc.
Morgantown, WV

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

Subjects: The study was conducted in twenty-one (21) normal, healthy non-smoking, male subjects. They were accepted into the study following informed consent, physical examination and blood and urine analysis. Nineteen subjects completed the clinical portion of the study.

Selection criteria,
Exclusion criteria,
& Restrictions: Please see Study #VERA-9669 for single-dose under fasting conditions above as mentioned earlier.

Washout period: Two weeks

Dose and Treatments:

Treatment A: 1x240 mg Verelan® SR Capsule (Lederle), lot #428-233, Exp 4/97, administered after complete ingestion of a high fat breakfast preceded by an overnight fast.

Treatment B: 1x240 mg verapamil HCl ER Capsule (Mylan), lot #2C004J, batch size -- . Capsules, administered after complete ingestion of a high fat breakfast preceded by an overnight fast.

Treatment C: 1x240 mg verapamil HCl ER capsule (Mylan), lot #2C004J, administered following an overnight fast.

Food and fluid intake: Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen C ingested the capsule with 240 mL of water. Subjects on regimen A and B ingested the capsules with 240 mL of water after complete ingestion of a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). Lunch and dinner were served at 5 and 10 hours, respectively, post-dose. Water was not permitted from 2 hours before and until 2 hours after dosing, but was allowed at all other times.

Blood samples: Ten mL (10) blood samples were collected at 0 (pre-dose) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, and 48 hours after dosing. Plasma samples were immediately frozen.

Assay Methodology: Same as study #VERA-9669 above.

Interday precision and accuracy: Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from 3.0% to 5.4% and 4.8% to 7.2%, for verapamil and norverapamil, respectively. The accuracy were 100.7% and 104.8% for verapamil and norverapamil, respectively.

Statistical Analysis

Cpeak for verapamil and norverapamil was determined by establishing the peak concentration for each subject. The areas under the plasma verapamil and norverapamil concentration versus time curves (AUCs) were calculated by using the linear trapezoidal rule.

VI. In Vivo Results:

This study was conducted from November 16, 1994 to December 17, 1996 in the facilities of the Clinical and Pharmacologic Research, Drug Study Unit, Morgantown, WV. Twenty-one healthy male volunteers were accepted for entry into the clinical phase of the study. Nineteen subjects successfully completed all three phases of the clinical portion of the study. Subject #4 and subject #12 withdrew due to personal reasons that were not study related. Subject #21 had analytical interference and was not included in the data, therefore, data for eighteen subjects were reported. There were three adverse events (3 subjects) observed during the study that were probably drug related. Subjects #1 (phase I), 5 (phase I) and 10 (phase III) experienced a headache. None of the subjects required treatment and none of the adverse effects prohibited subjects from completing the study.

The plasma concentrations and pharmacokinetics parameters for verapamil and norverapamil are summarized in Tables III and IV

Table III

Mean Plasma Verapamil Concentrations and Pharmacokinetics Parameters Following an Oral Dose of 240 mg Verapamil HCl ER (1x240 mg Capsule) Under Fasting and Nonfasting Conditions
(N=18)

Time hr	Treatment A Verelan® Lot #428-233 Nonfasting ng/mL (CV)	Treatment B Mylan Lot #2C004J Nonfasting ng/mL (CV)	Treatment C Mylan Lot #2C004J Fasting ng/mL (CV)
0	0	0	0
1	4.99 (103.1)	5.71 (115.0)	17.40 (49.4)
2	17.23 (63.0)	15.77 (45.4)	15.40 (50.7)
3	24.34 (54.8)	24.16 (42.8)	16.75 (53.5)
4	28.95 (48.1)	29.38 (50.0)	23.19 (70.0)
5	40.91 (48.7)	34.92 (52.6)	30.86 (74.6)
6	65.37 (45.5)	51.72 (47.7)	57.88 (54.1)
7	78.01 (65.5)	64.63 (45.8)	67.53 (45.2)
8	75.07 (49.7)	68.09 (44.4)	69.72 (43.2)
9	73.15 (38.2)	67.42 (40.9)	71.17 (34.4)
10	68.85 (35.4)	63.26 (37.8)	70.83 (34.2)
11	72.69 (37.9)	62.57 (33.9)	71.61 (42.2)
12	65.78 (36.5)	56.19 (33.7)	62.91 (41.7)
14	53.06 (36.3)	47.05 (34.3)	53.23 (43.8)
16	44.11 (37.4)	40.92 (38.1)	43.94 (49.1)
24	32.17 (40.5)	32.14 (38.2)	32.08 (47.1)
36	10.18 (52.7)	11.69 (53.4)	10.50 (54.7)
48	4.09 (82.5)	5.14 (75.0)	4.20 (78.6)

				B/A
AUC(0-t) (ng.hr/mL)	1420.9 (38.9)	1329.7 (35.4)	1394.3 (40.6)	0.94
AUCinf (ng.hr/mL)	1466.8 (35.3)	1428.7 (25.2)	1470.9 (39.3)	0.97
Cpeak(ng/mL)	89.7 (56.5)	77.0 (41.3)	83.3 (41.0)	0.86
Tpeak (hr)	9.33	8.78	9.00	
T1/2 (hr)	9.34	10.1	9.27	

Kel (hr^{-1})	0.078	0.074	0.08

1. The verapamil plasma levels peaked at 7 and 8 hours for the reference and the test products, respectively, under nonfasting conditions and at 11 hours for the test product under fasting conditions.

2. For Mylan's test product, the mean AUC(0-t), AUCinf and Cpeak values were 6.4%, 2.6%, 14.2%, lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cpeak under nonfasting conditions. The ratios of the least-squares means of the log-transformed parameters are as following:

AUC(0-T)	95.3
AUCinf	97.0
Cmax	91.0

The ratios of least-squares means of the log-transformed parameters AUC(0-t), AUCinf and Cpeak for verapamil meet the criteria of 80-125%.

3. For the test product, the mean Cmax value after dosing with food was about 92.4% of the value reported in the fasting state.

Table IV

Mean Plasma Norverapamil Concentrations and Pharmacokinetics Parameters Following an Oral Dose of 240 mg Verapamil HCl ER (1x240 mg Capsule) Under Fasting and Nonfasting Conditions

(N=18)

Time hr	Treatment A Verelan® Lot #428-233 Nonfasting ng/mL (CV)	Treatment B Mylan Lot #2C004J Nonfasting ng/mL (CV)	Treatment C Mylan Lot #2C004J Fasting ng/mL (CV)
0	0	0	0
1	1.74 (124.0)	1.65 (174.5)	11.44 (40.9)
2	10.22 (44.9)	10.29 (43.5)	14.55 (27.4)
3	17.82 (41.7)	18.02 (31.6)	17.44 (29.7)

4	25.01 (38.3)	24.39 (31.1)	21.65 (34.9)
5	35.49 (36.6)	30.87 (29.5)	26.71 (37.0)
6	53.79 (33.5)	44.99 (30.2)	39.63 (35.4)
7	67.34 (47.2)	52.56 (29.2)	47.75 (31.7)
8	71.82 (41.9)	58.60 (28.6)	54.15 (31.7)
9	73.15 (37.3)	62.22 (28.5)	57.56 (27.5)
10	72.61 (34.5)	62.99 (28.9)	60.82 (27.6)
11	74.46 (36.2)	63.08 (24.5)	61.96 (27.6)
12	72.71 (32.9)	60.89 (27.3)	60.70 (25.9)
14	65.22 (32.7)	56.32 (26.3)	57.67 (26.4)
16	58.09 (32.2)	51.48 (29.1)	51.43 (27.6)
24	45.61 (29.3)	42.53 (27.3)	42.51 (29.8)
36	20.05 (36.3)	20.33 (35.3)	19.87 (39.4)
48	9.73 (39.5)	10.33 (50.6)	9.66 (46.7)

				B/A
AUC(0-t)				
(ng.hr/mL)	1770.2 (31.9)	1581.6 (24.8)	1597.6 (26.2)	0.89
AUCinf				
(ng.hr/mL)	1886.3 (29.3)	1794.5 (26.6)	1735.4 (27.7)	0.97
Cpeak(ng/mL)	79.3 (40.6)	66.9 (26.4)	66.5 (25.6)	0.86
Tpeak (hr)	10.4	10.2	11.0	
T1/2 (hr)	10.9	12.2	10.9	
Kel (hr^{-1})	0.066	0.061	0.066	

1. The norverapamil plasma levels peaked at 11 hours for both the reference and the test products, under nonfasting conditions and for the test product under fasting conditions.

2. For Mylan's test product, the mean AUC(0-t), AUCinf and Cpeak values were 10.7%, 4.8%, 15.6%, lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cpeak under nonfasting conditions. The ratios of the least-squares means of the log-transformed parameters are as following:

AUC(0-T)	91.2
AUCinf	95.5
Cmax	88.4

The ratios of least-squares means of the log-transformed parameters AUC(0-t), AUCinf and Cpeak for norverapamil meet the

criteria of 80-125%.

3. For the test product, the mean Cmax value after dosing with food was about the same as reported in the fasting state.

VII. Study #VERA-9674, Multiple-dose Bioequivalence study of Verapamil HCl 240 mg ER Capsules

The objective of the study was to assess the bioavailablity at steady-state of verapamil HCl 240 mg ER capsule (Mylan) as compared to Verelan[R] SR 240 mg Capsule (Lederle) following once-a-day dosing of each formulation for seven days.

Clinical site: Clinical and Pharmacologic Research Inc. Morgantown, WV.

Analytical site:

Study date: Clinical phase: January 27,1997 - March 21, 1997
Analytical phase: February 25, 1997 - April 17, 1997

Study design: Two-way crossover, multiple-dose study

Subjects: Thirty-eight (38) male subjects were accepted for entry into the clinical portion of the study. Thirty-four (34) subjects successfully completed both phases of the clinical portion of the study. The clinic portion of the study was conducted in two groups. Group A consisted of volunteers 1-20, Group B consisted of volunteers 21-38. The dosing dates for this study were as following:

	Phase I	Phase II
Group A	January 27	February 18, 1997
Group B	March 1	March 22, 1997

Washout period: Two weeks

Subject welfare: Vital signs (blood pressure, pulse rate and respiration) were measured hourly for the first 12 hours after the first and seventh doses. Lead II ECGs, sitting blood pressure and pulse rate were measured before the morning dose on days 1 and 7, for the first eight hours after dosing and then at 12 and 24 hours on days 1 and 7.

Selection criteria,
Exclusion criteria,
& Restrictions: Please see Study #VERA-9669 for single-dose under fasting conditions as mentioned previously.

Dose and treatment:

Treatment A
Day 1-7: 1x240 mg Verapamil HCl ER Capsule (Mylan), lot #2C004J administered with 240 mL of water, following a 10 hours overnight fast.
Treatment B
Days 1-7: 1x240 mg Verelan® SR Capsule (Lederle), lot #428-233 administered with 240 mL of water, following a 10 hours overnight fast.

Food and fluid intake: Subjects fasted for ten hours prior to dosing. Meals for days 1 through 6 were served at 2, 5, 10 and 14 hours, respectively, for breakfast, lunch, dinner and snacks. Relative to 7th dose subjects received a standard meal 5 hours post-dose following by an evening meal 10 hours after dosing and snacks at appropriate times thereafter. Water was not permitted from 2 hours before and until 2 hours after the 7th dose, but was allowed at all other times.

Blood samples: Blood samples were collected during each study period at: Day 1: 0 hour (pre-drug)
Day 5: 0 hour (pre-drug)
Day 6: 0 hour (pre-drug)
Day 7: 0 hour (pre-drug) and at 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, 11, 12, 14, 16, 20 and 24 hours following drug administration.

Assay Methodology: Same as study #VERA-9669 above.

Interday precision and accuracy: Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from 4.0% to 4.6% and 4.7% to 5.1%, for verapamil and norverapamil, respectively. The accuracy were 100.1% and 99.7% for verapamil and norverapamil, respectively.

Statistical Analysis:

Statistical analysis was performed using SAS-GLM. ANOVA was performed using GLM. Pharmacokinetics parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval for the pharmacokinetics parameters. An analysis of variance was performed to assess the group effect. A model with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, treatments and periods was performed.

VIII. In Vivo Results

Thirty-eight (38) subjects enrolled in this study in two groups. Thirty-four subjects completed the study. Group A consisted of volunteers 1-20, Group B consisted of volunteers 21-38. Subject #1 was withdrawn in period II due to protocol violation (tobacco products found on his person during the study). Subjects #26 and #36 were discontinued from the study during period II due to unacceptable behavior. Subject #25 dropped out of the study during period II due to personal reasons which were related to the length of the study confinement. There were 8 subjects who experienced 14 adverse events. Of those, 10 adverse events were reported as probably or possibly drug related [headache (5), dizziness (1), upset stomach (2) and (1) constipation]. The results indicated that the incidence of adverse experiences were similar between the test and reference products. There were no serious or life-threatening medical events reported in the study.

The plasma concentrations and pharmacokinetic parameters for verapamil and norverapamil are summarized in Tables V and VI.

Table V

Mean Verapamil Plasma Concentrations and Pharmacokinetics Parameters Following a Multiple Dosing (7x240 mg) of Verapamil HCl ER 240 mg Capsules

(N=34)

Time hr	Treatment A Mylan Lot #2C004J ng/mL (CV)	Treatment B Verelan® Lot #428-233 ng/mL (CV)
0	0.00	0.00
96	55.38 (45.6)	52.22 (40.9)
120	60.29 (41.5)	55.86 (38.3)
144	59.13 (40.3)	57.44 (37.6)
145	94.73 (38.1)	92.96 (37.2)
146	89.91 (36.4)	90.01 (34.4)
147	88.16 (39.8)	93.16 (34.7)
148	94.63 (45.3)	98.37 (34.0)
149	101.77 (42.2)	109.15 (33.5)
150	132.61 (39.0)	130.25 (34.5)
151	138.66 (41.8)	132.74 (36.6)
152	140.83 (40.8)	133.88 (34.8)
153	140.39 (39.3)	133.49 (34.1)
154	129.10 (42.9)	127.93 (33.3)
155	130.21 (38.2)	123.97 (32.4)
156	119.65 (37.6)	114.94 (32.6)
158	100.42 (37.5)	98.89 (34.6)
162	87.14 (42.2)	84.00 (32.9)
164	64.87 (44.3)	60.34 (37.4)
168	63.46 (46.9)	57.27 (36.3)

			90% CI
AUC(0-24)(ng.hr/mL)	2338.7 (37.3)	2272.7 (31.9)	
Cpeak (ng/mL)	154.2 (36.6)	149.5 (32.5)	
Cmin (ng/mL)	53.1 (46.2)	53.7 (37.3)	

Tpeak (hr)	8.3		7.5	
Css (ng/mL)	97.4	(37.3)	94.7	(31.9)
Fluct1 (%)	108.0	(37.2)	104.0	(25.5)
Fluct2 (%)	217.0	(70.5)	197.0	(41.7)

LnAUC(0-24)	94-109%
LnCpeak	94-112%

*Fluct1 = (Cpeak-Cmin)/Css*100
**Fluct2 = (Cpeak-Cmin)/Cmin*100
Cmin = Min. Conc. from time range 144-168 hours
Css = AUC/24

1. The plasma verapamil levels peaked at 152 hours for both the test and the reference products.

2. For verapamil, the least squares means for AUC(0-24) and Cpeak values were 3.2% and 3.6% higher, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

3. Additional analysis of variance was performed by the reviewer. The following model

Y = SEQ SUBJ(SEQ) PER TRT; (whereas period = 4)

was employed in the statistical analysis of the study. The following 90% confidence intervals for LnAUC(0-24) and LnCpeak were obtained:

Verapamil

LnAUC(0-24)	94.1-108.6%
LnCpeak	94.2-112.0%

The 90% confidence intervals for the above pharmacokinetics parameters calculated using the above model remained within the acceptable range of 80-125%.

Table VI

Mean Norverapamil Plasma Concentrations and Pharmacokinetics

Parameters Following a Multiple Dosing (7x240 mg) of Verapamil HCl ER 240 mg Capsules

(N=34)

Time hr	Treatment A Mylan Lot #2C004J ng/mL (CV)	Treatment B Verelan® Lot #428-233 ng/mL (CV)
0	0.00	0.00
96	70.45 (30.8)	67.07 (29.5)
120	73.61 (29.1)	68.60 (29.2)
144	72.42 (30.4)	68.55 (27.9)
145	88.46 (28.8)	85.89 (26.8)
146	92.15 (28.1)	89.78 (25.6)
147	92.20 (29.0)	92.71 (25.4)
148	94.48 (29.3)	96.50 (25.7)
149	97.57 (28.2)	101.78 (25.5)
150	107.34 (25.6)	109.08 (24.4)
151	112.18 (26.0)	114.35 (25.1)
152	116.27 (26.4)	116.71 (24.8)
153	118.48 (26.2)	118.52 (23.7)
154	112.96 (31.9)	116.59 (23.8)
155	114.84 (26.9)	113.52 (24.7)
156	111.30 (26.2)	110.29 (24.5)
158	103.21 (26.3)	104.06 (25.3)
162	94.83 (29.2)	94.52 (24.8)
164	76.98 (30.9)	73.31 (27.5)
168	77.26 (33.3)	72.25 (28.0)

			90% CI
AUC(0-24)(ng.hr/mL)	2303.4 (26.6)	2284.6 (24.3)	
Cpeak (ng/mL)	124.4 (24.8)	124.1 (23.2)	
Cmin (ng/mL)	66.9 (36.0)	66.7 (27.8)	
Tpeak (hr)	9.9	8.6	
Css (ng/mL)	96.0 (26.6)	95.2 (24.3)	
Fluct1 (%)	61.8 (35.4)	61.7 (23.4)	
Fluct2 (%)	87.5 (44.4)	91.4 (35.7)	
LnAUC(0-24)			95-105%
LnCpeak			95-105%

*Fluct1 = (Cpeak-Cmin)/Css*100

**Fluct2 = (Cpeak-Cmin)/Cmin*100

Cmin = Min. Conc. from time range 144-168 hours
Css = AUC/24

1. The plasma norverapamil levels peaked at 153 hours for both the test and the reference products.

2. For norverapamil, the least squares means for AUC(0-24) and Cpeak values were 0.9% and 0.4% higher, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for each of the above parameters are within the acceptable range of

3. Additional analysis of variance was performed by the reviewer. The following model

Y = SEQ SUBJ(SEQ) PER TRT; (whereas period = 4)

was employed in the statistical analysis of the study, resulted in the following 90% confidence intervals for LnAUC(0-24) and LnCpeak:

Norverapamil

LnAUC(0-24)	95.1-104.9%
LnCpeak	94.5-105.2%

The 90% confidence intervals for the above pharmacokinetics parameters calculated using the above model remained within the acceptable range of

IX. Formulation:

Mylan's formulation for its verapamil HCl ER 240 mg capsule is shown in Table VII.

X. In vitro Dissolution Testing:

Method:	USP 23 apparatus II (paddle) at 100 rpm
Medium:	900 mL of 0.1N HCl.
Sample Times:	2, 4, 8 and 24 hours
Number of Capsules:	12

Test Product: Mylan's Verapamil HCl ER capsules, 240 mg
Lot #2C004J

Reference Product: Lederle's Verelan^{R} SR capsule, 240 mg
lot #428-233

The dissolution testing results are presented in Table VIII.

XI. Comments:

1. The firm's single-dose bioequivalence study #VERA-9669 under fasting conditions, conducted on its 240 mg verapamil HCl ER capsule is acceptable. The two study drugs did not differ significantly with respect to mean values for any of the pharmacokinetics parameters. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCpeak are within the acceptable range of ; for verapamil and norverapamil.

2. The firm's single-dose bioequivalence study #VERA-9612 under fasting and nonfasting conditions, conducted on its 240 mg verapamil HCl ER capsule is acceptable. The ratios of the test mean to the reference mean for AUC(0-t), AUCinf and Cpeak are within the acceptable range of 0.8-1.2 for verapamil and norverapamil under nonfasting conditions.

3. The firm's multiple-dose bioequivalence study #VERA-9674 under fasting conditions, conducted on its 240 mg verapamil HCl ER capsule is acceptable. The 90% confidence intervals for LnAUC(0-24) and LnCpeak are within the acceptable range of 80-125% for verapamil and norverapamil.

4. The in vitro dissolution testing for the test product 240 mg verapamil HCl ER capsules is acceptable.

XII. Deficiency Comment:

One of the approved methods of administration for the reference listed drug is to open the capsule and sprinkle its contents on a spoonful of applesauce. Therefore, the completion of a bioequivalence study to demonstrate bioequivalence between the generic version and the reference listed drug when administered as sprinkled on applesauce is required.

The firm is advised to submit a sprinkling bioequivalence study. A study to demonstrate bioequivalence of the generic version versus the innovator product (Verelan^{R}) when capsule contents are sprinkled on applesauce. The recommended design is, two-treatment, two-period, two sequence, crossover comparing the test product with the reference product sprinkled on one tablespoon of applesauce under fasting condition.

XIII. Recommendations:

1. The single-dose bioequivalence study #VERA-9669, conducted by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended Release 240 mg Capsule, lot #2C004J, comparing it to Verelan^{R} SR 240 mg Capsule manufactured by Lederle, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment.

2. The single-dose post-prandial bioequivalence study #VERA-9612, conducted by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended Release 240 mg Capsule, lot #2C004J, comparing it to Verelan^{R} SR 240 mg Capsule manufactured by Lederle, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment.

3. The multiple-dose steady-state bioequivalence study #VERA-9674, conducted by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended Release 240 mg Capsule, lot #2C004J, comparing it to Verelan^{R} SR 240 mg Capsule manufactured by Lederle, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment.

4. The dissolution testing conducting by Mylan Pharmaceuticals Inc., on its verapamil HCl ER 240 mg Capsules, lot #2C004J is acceptable. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 100 rpm. Based on the submitted data the following tentative specifications are recommended:

2	hours
4	hours
8	hours
24	hours

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramadevi Mhatre Date: 11/20/97

Concur: Rabinda Patnaik Date: 11/20/97
Rabinda Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Mmakary/8-20-97, 11-20-97, wp 75138SD.597

Table VIII In Vitro Dissolution Testing

Drug (Generic Name):Verapamil ER
Dose Strength: 240 mg Capsules
ANDA No.:75-138
Firm: Mylan Pharmaceuticals Inc.
Submission Date: May 29, 1997
File Name: 75138SD.597

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 100
No. Units Tested: 12
Medium:900 mL of 0.1N HCl
Specifications: 2 hours between 10% and 25%
4 hours between 15% and 40%
8 hours between 35% and 70%
24 hours
Reference Drug: Lederle's Verelan SR Capsules, 240 mg
Assay Methodology

II. Results of In Vitro Dissolution Testing:

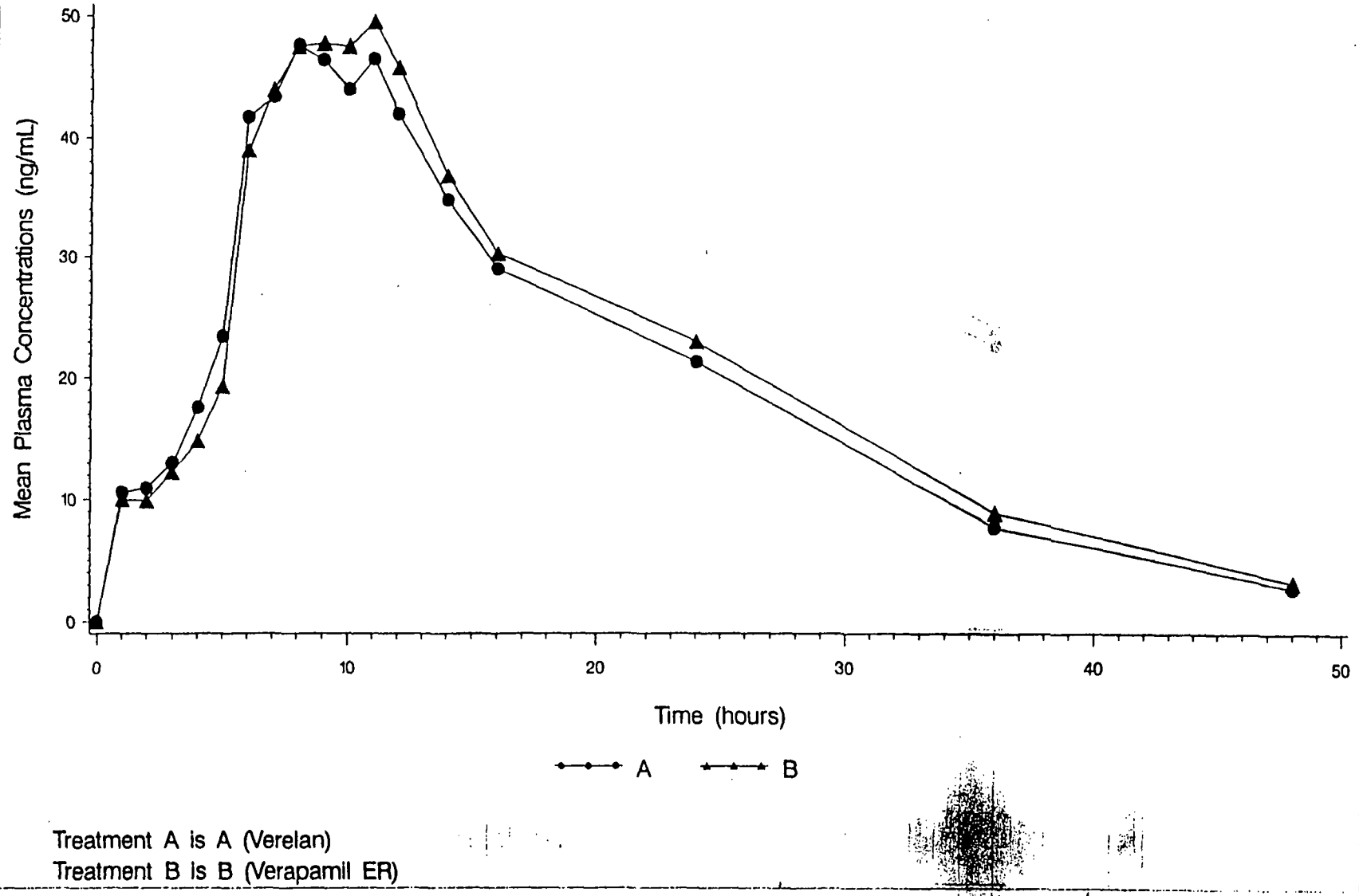
Sampling Times (hr)	Test Product Lot #2C004J Strength(mg) 240			Reference Product Lot #428-233 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
2	17		7.3	18		7.7
4	31		4.3	32		4.1
8	54		3.6	63		3.1
24	94		2.7	95		2.2

VERAPAMIL ER (VERA–9669)

Total Dose: 240 mg (1x240mg Capsule), Study Type: Fasting

Mean Verapamil Plasma Concentrations

N=46



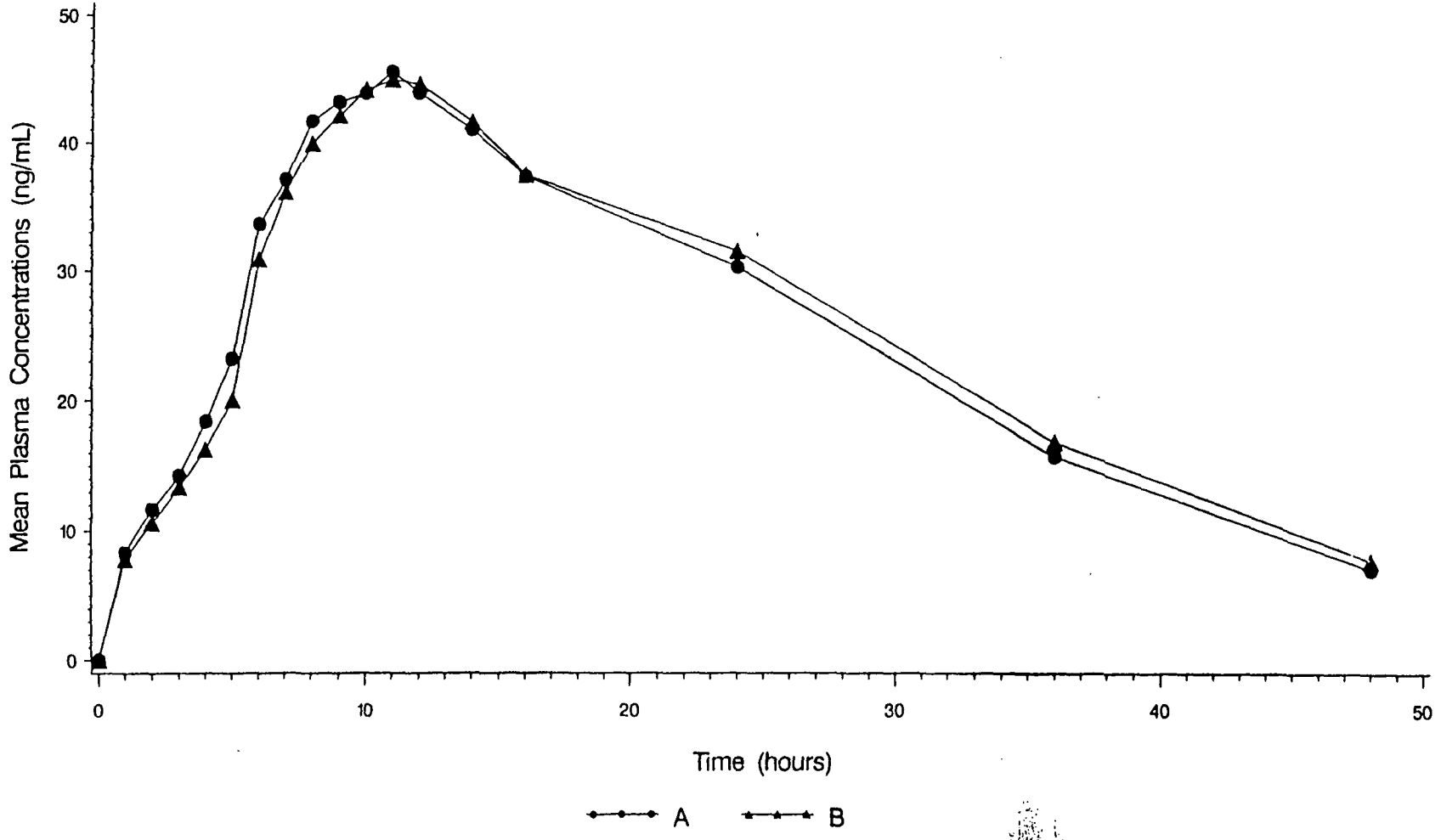
Treatment A is A (Verelan)
Treatment B is B (Verapamil ER)

VERAPAMIL ER (VERA–9669)

Total Dose: 240 mg (1x240mg Capsule), Study Type: Fasting

Mean Norverapamil Plasma Concentrations

N= 46



Treatment A is A (Verelan)

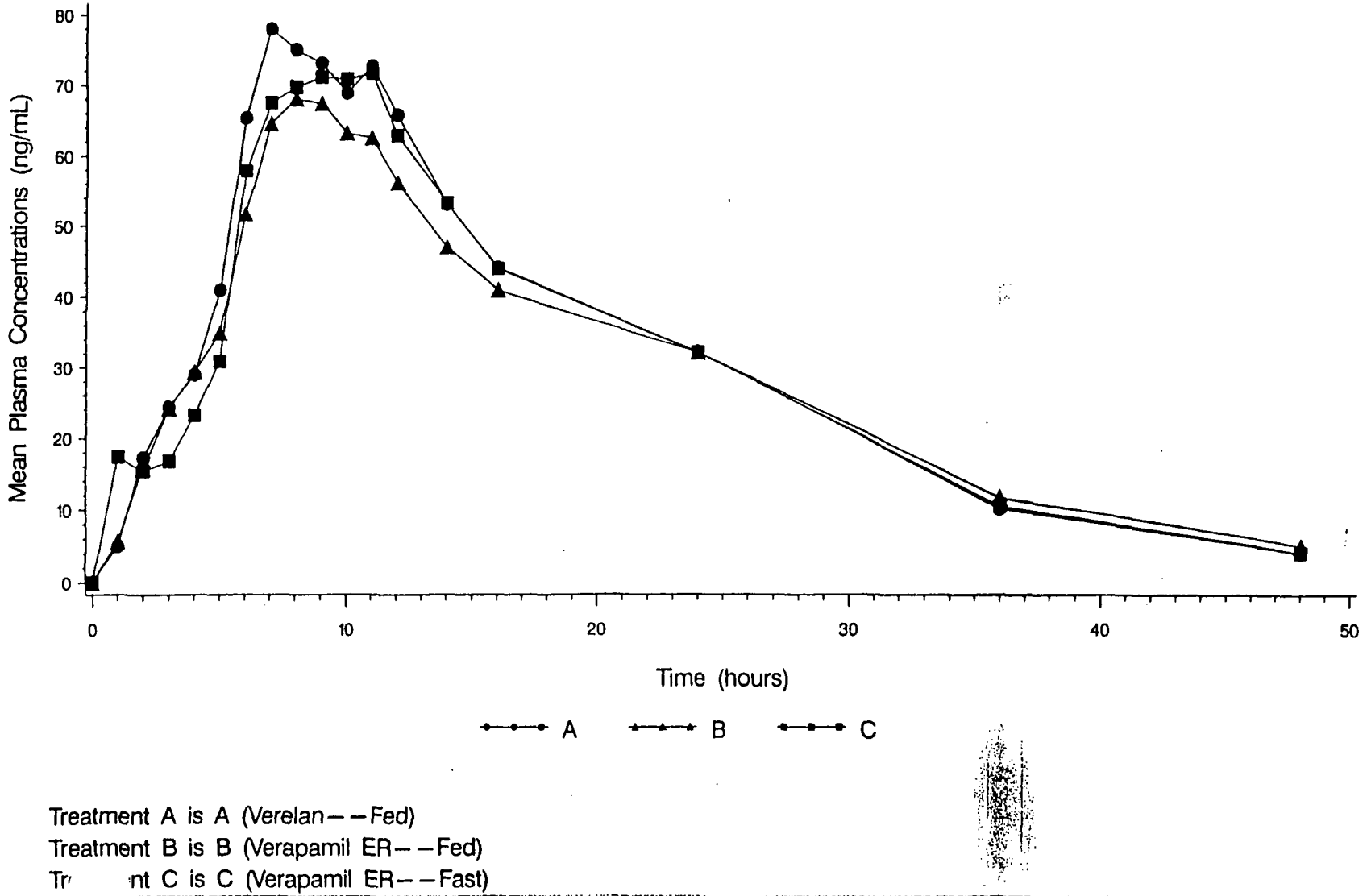
Treatment B is B (Verapamil ER)

VERAPAMIL ER (VERA–9612)

Total Dose: 240 mg (1x240mg Capsule), Study Type: Fed

Mean Verapamil Plasma Concentrations

N= 18



Treatment A is A (Verelan––Fed)
Treatment B is B (Verapamil ER––Fed)
Tr nt C is C (Verapamil ER––Fast)

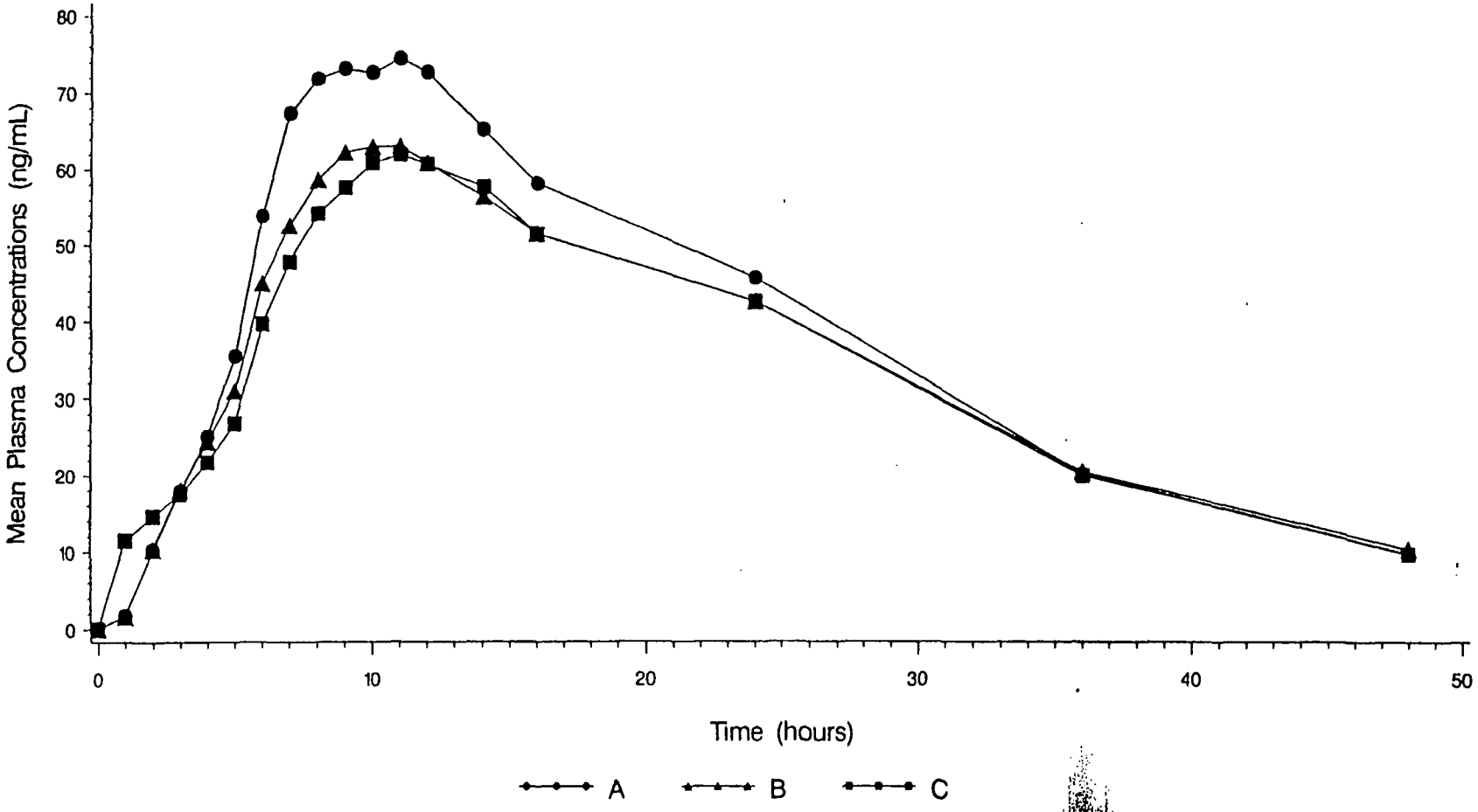
3231

VERAPAMIL ER (VERA–9612)

Total Dose: 240 mg (1x240mg Capsule), Study Type: Fed

Mean Norverapamil Plasma Concentrations

N= 18



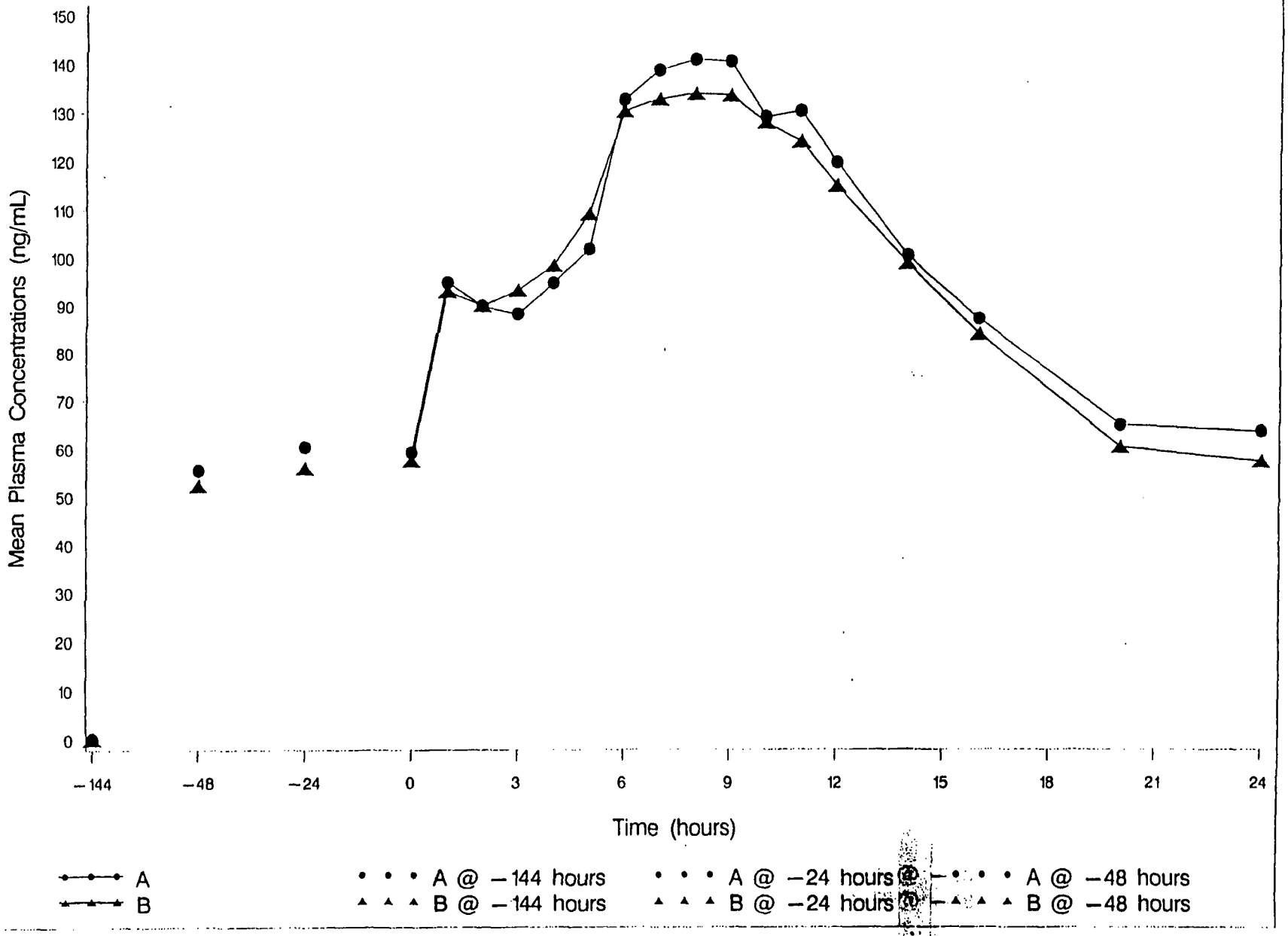
Treatment A is A (Verelan– –Fed)

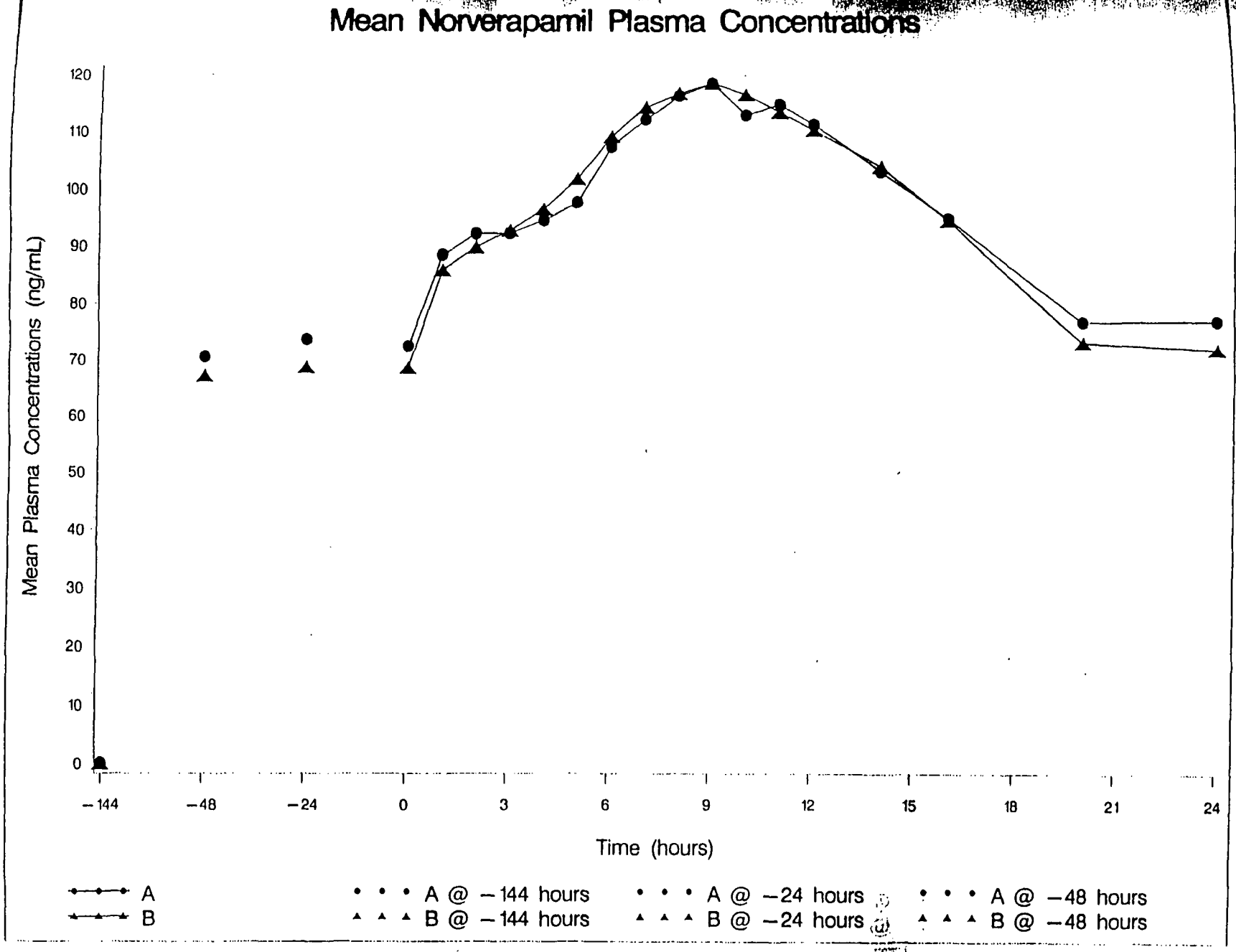
Treatment B is B (Verapamil ER– –Fed)

Treatment C is C (Verapamil ER– –Fast)

VERAPAMIL ER (VERA–9674)

Mean Verapamil Plasma Concentrations





ATTACHMENT 1A