

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-072

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-072

APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Verapamil HCl Extended-Release Tablets USP,
120 mg and 240 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of simulated gastric fluid (SGF) without enzyme (first hour) and 900 mL of simulated intestinal fluid (SIF) without enzyme (second hour and thereafter) at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specifications:

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



The Art of Leadership...
The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

January 13, 1999

ANDA ONLY AMENDMENT

AB

Mr. Doug Sporn
Director, Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **ANDA 75-072**
Verapamil Hydrochloride Extended-Release Tablets USP,
120 mg and 240 mg

Subject: **BIOEQUIVALENCE AMENDMENT**
Reconsideration of Decision

Dear Mr. Sporn:

In accordance with 21 CFR 314.75, we request reconsideration be given to a decision rendered in a letter dated October 26, 1998 signed by Dr. Dale Conner, Director, Division of Bioequivalence concerning three (3) review comments on bioequivalence studies in our pending Abbreviated New Drug Application 75-072 for Verapamil HCl ER Tablets, USP, 120 mg and 240 mg.

In this correspondence, the Division has concluded that the fasting studies conducted for both the 120- and 240 mg strength tablets and steady state study conducted for the 240 mg tablets are all acceptable. However, all three comments address the same issue: the acceptability of the log-transformed AUC_{0-t} observed for verapamil in the effect-of-food study conducted for the 240 mg dosage strength (both C_{max} and AUC_{0-inf} for verapamil and C_{max} , AUC_{0-t} and AUC_{0-inf} for norverapamil are acceptable).

The issue has been the interpretation of the analysis and calculation of the pharmacokinetic parameter $\ln AUC_{0-t}$ for the effect-of-food study for which we now introduce new information. We now request that reconsideration be given to the decision of the Division of Bioequivalence based on this amendment and that Dr. Roger Williams be included in these deliberations. The basis for reconsideration of this decision is as follows:

1. **Corrected $\ln AUC_{0-t}$ ratio is 125% using all data points.** In the original decision we had calculated the ratio of least square means of $\ln AUC_{0-t}$ to be 1.254. The reviewer recalculated this ratio to be 1.257 by excluding nonsignificant first-order carryover effects from the model.

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JAN 14 1999

GENERIC DRUGS

We only recently determined (new information) that a data transcription error occurred in a single reported plasma concentration (subject #2, 24 hours, test treatment under fed conditions). Using this corrected value the recalculated ratio for $\ln AUC_{0-t}$ is 1.2518 (analysis attached in tab RECALCULATED AUC).

The data transcription error corrected an entry of 58.13 to 49.23 ng/mL for subject #2, 24 hours, test treatment for the verapamil analyte. The fact that such a relatively small error causes such a large difference in calculated ratio (1.257 vs. 1.2518) is a reflection of the relatively low number of subjects completing this study (20- and 19 subjects for the test and reference formulations respectively) and the documented high variability of the metabolism of the drug substance itself. We believe this result meets the limits of 80-125% when consideration is given to significant figures.

2. **Ratio of $\ln AUC_{0-t}$ is 124.0% dropping one outlying data point.** As reflected in our previous amendments of December 10, 1997 and June 25, 1998, dropping a single outlying concentration value, leads to a $\ln AUC_{0-t}$ of 1.2401. The outlying data point is subject #2, 24 hours, reference treatment under fed conditions.
3. **Dropping the questionable value is justified based on sound scientific evidence.** The reviewer had a two-part approach to dismissing our scientific rationale in support of our position that the reference result for verapamil for subject #2 at 24 hours is anomalous. As shown below, each part is subject to a valid alternate interpretation.
 - a) The Division compared the verapamil profile of subject #2 to other subjects' profiles and indicated that subject #20 had a similar profile and thus subject 2 could not be considered an outlier. We agree that subject #2 is not an outlier – the outlier is subject #2's single plasma value at 24 hours for the reference treatment. We had used a comparison of verapamil to norverapamil profiles as a means to determine candidates for further examination for outliers. The consistency of profiles, or lack thereof, was done by examination of AUC_{0-t} to avoid arbitrary visual examination. Subject #20, for example, has a verapamil profile similar to subject #2's, but while the norverapamil and verapamil profiles of subject #20 are similar for all three treatments, such is not the case for Subject #2 – the norverapamil and verapamil profiles for the reference formulation are inconsistent while they are similar for the test formulation under both fasting and nonfasting conditions.
 - b) The Division asserts that the “[I]ntrasubject variability in the rate of metabolism of verapamil to norverapamil *may* produce different values for norverapamil from hour to hour” (emphasis added) and therefore rejected our use of norverapamil/verapamil comparisons to determine potential outliers. As noted in item (3a) above, AUC_{0-t} comparisons of verapamil to norverapamil were used as a means to determine if there were any profiles that were inconsistent. That this exercise showed that only 3 out of 22 subjects had anomalous behavior attests to the usefulness of this approach. Nevertheless, this comparison only identified these 3 subjects as candidates for further examination. It was only after we examined the profiles and analytical history of these 3 subjects that the 24 hour time point for subject #2 received further examination. During the analytical

testing, the 24 hour time point for verapamil for the test formulation was flagged as an outlier and retested with results supporting the original value. A visual examination of the profiles for subject #2 for each treatment clearly indicates slight differences between the results for verapamil and norverapamil at each time point, however, these differences don't exceed a few percent except for the dramatic difference in the verapamil/norverapamil profiles for the reference treatment at 24 hours. No other subjects' profile comparisons reach this difference.

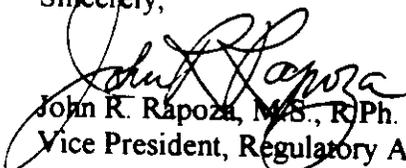
4. **The clinical relevance of a food effect is controversial.** Although the innovator's labeling includes directions to take the product with food, it has been pointed out that that this information is based on a small study. Several studies have shown that C_{max} , $t_{1/2}$ and AUC, as well as blood pressure and ECG effects are similar under fasting and nonfasting conditions, while T_{max} is prolonged. The authors^{1,2,3} of these studies concluded that label cautions regarding 'taking [Verapamil SR] with food therefore appear to be unnecessary'.

Through various forums, the Agency has indicated it is willing to revise its approach to making bioequivalence assessments, i.e., making its assessments more science-based. We encourage this approach for drug products based on highly variable drug substances. In this case, it is well-known that verapamil is a highly variable drug. Duramed's pending application contains four (4) bioequivalence studies, each measuring verapamil and its metabolite, norverapamil. All four (4) studies meet the established 80-125% limits for log transformed pharmacokinetic parameters, with the lone AUC_{0-t} parameter for the nonfasting study being about 125%. Clinically, this finding is insignificant. Scientifically, this value is an estimate based on a highly variable drug.

We urge reconsideration of your decision and acceptance of our position that the best estimate of the ratio of $\ln AUC_{0-t}$ is 125% for verapamil under fasting conditions.

If you have any questions, please feel free to contact Mr. Ken Phelps at (513) 458-7325, or the undersigned at (513) 458-7274.

Sincerely,


John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Encl. FDA Form 356H
Desk copy: Dr. Dale Conner

¹ Conway, E.L. et al. "Influence of food on the bioavailability of a sustained-release verapamil preparation," *J Pharm Sci*, 79(3), 1990, 238-231
² HHoon, T.J. et al. "Impact of food on the pharmacokinetics and electrocardiographic effects of sustained release verapamil in normal subjects," *Am J Cardiol*, 70, 1992, 1072-1076
³ SK Gupta et al. "The effect of food, time of dosing, and body position on the pharmacokinetics and pharmacodynamics of verapamil and norverapamil," *J Clin Pharmacol*, 35(11), 1995, 1083-93

Verapamil HCl ER Tablet
120 mg and 240 mg
ANDA # 75-072
Reviewer: Moheb H. Makary
W 75072SD.199

Duramed Pharmaceuticals, Inc.
Cincinnati, Ohio
Submission Date:
January 13, 1999

Review of an Amendment

I. Objective:

In this amendment, the firm is requesting reconsideration of a decision regarding its pending ANDA #75-072 for Verapamil HCl ER Tablets, 120 mg and 240 mg (letter dated October 26, 1998).

The DBE has concluded that the fasting studies conducted on both the 120 mg and 240 mg tablets and the steady-state study conducted on the 240 mg tablets were found acceptable. However, the post-prandial bioequivalence study #950281, conducted on Verapamil HCl ER 240 mg Tablets was found unacceptable since the ratio for LnAUC(0-t) exceeded the limits of 0.8-1.25 under nonfasting conditions.

Comment 1

By using all of the reported data (the actual draw time) for the post-prandial bioequivalence study #950281 conducted on Verapamil HCl ER Tablet, 240 mg, and employing the following model,

$$Y = \text{seq subj}(\text{seq}) \text{ per trt};$$

the resulting ratios of least-squares means of the log-transformed parameters for verapamil were:

LnAUC	1.257
LnAUCinf	1.209
LnCmax	1.243

The ratio for AUC(0-t) parameter exceeds limits of 0.80-1.25%. Therefore, the study was found unacceptable.

In this amendment, the firm introduces new information. A data transcription error occurred in a single reported

plasma concentration for subject #2 at 24 hours, test treatment under nonfasting conditions for the verapamil analyte. The data transcription error corrected an entry of 58.13 to 49.23 ng/mL for the above mentioned plasma concentration time point.

After using this corrected value and recalculation of AUC(0-t) for subject #2 by the reviewer, the resulting ratios of least-squares means of the log-transformed parameters for verapamil are:

LnAUC	1.25
LnAUCinf	1.21
LnCmax	1.23

The ratios of the least squares geometric means are within the acceptable range of 0.80-1.25 for AUC(0-t), AUCinf and Cmax. Therefore, the study is acceptable.

Reply to Comment 1

The reviewer acknowledged the error. The firm's response to the comment is acceptable.

II. Recommendations:

1. The single-dose fasting bioequivalence study #941081, conducted by Duramed Pharmaceuticals, Inc., on its Verapamil HCl Extended-Release (ER) Tablet, 240 mg, lot #950301, comparing it to Isoptin^R SR Tablet, 240 mg, manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Verapamil HCl ER Tablet, 240 mg, is bioequivalent to Knoll's Isoptin^R SR Tablet, 240 mg.

2. The single-dose post-prandial bioequivalence study #950281, conducted by Duramed Pharmaceuticals, Inc., on its Verapamil HCl ER Tablet, 240 mg, lot #950301, comparing it to Isoptin^R SR Tablet, 240 mg, manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Verapamil HCl ER Tablet, 240 mg, is bioequivalent to Knoll's Isoptin^R SR Tablet, 240 mg.

3. The multiple-dose steady-state bioequivalence study #950282, conducted by Duramed Pharmaceuticals, Inc., on its Verapamil HCl ER Tablet, 240 mg, lot #950301, comparing it

to Isoptin^R SR Tablet, 240 mg, manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Verapamil HCl ER Tablet, 240 mg, is bioequivalent to Knoll's Isoptin^R SR Tablet, 240 mg.

4. The single-dose fasting bioequivalence study #950257, conducted by Duramed Pharmaceuticals, Inc., on its Verapamil HCl (ER) Tablet, 120 mg, lot #960702S, comparing it to Isoptin^R SR Tablet, 120 mg, manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Verapamil HCl ER Tablet, 120 mg, is bioequivalent to Knoll's Isoptin^R SR Tablet, 120 mg.

5. The dissolution testing conducted by Duramed Pharmaceuticals, Inc., on its Verapamil HCl ER Tablets, 240 mg and 120 mg, lot #950301 and lot #960702S, respectively, is acceptable.

6. The dissolution testing should be conducted in 900 mL of simulated gastric fluid (SGF) without enzyme (first hour) and 900 mL of simulated intestinal fluid (SIF) without enzyme (second hour and thereafter) at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specifications:

The firm should be informed of the above recommendations.

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

Date: 2/26/99

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

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Date: 3/1/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-072

APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Verapamil HCl Extended-Release Tablets USP,
120 mg and 240 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of simulated gastric fluid (SGF) without enzyme (first hour) and 900 mL of simulated intestinal fluid (SIF) without enzyme (second hour and thereafter) at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specifications:

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,

/S/

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

4.1
James C.

OCT 26 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-072

APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Verapamil HCl ER Tablets, 120 mg, 180 mg and 240 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You propose that the reference result for verapamil for subject #2 at 24 hours is anomalous. This argument is unacceptable for the following reasons. In the single-dose post-prandial bioequivalence study #950281, some subjects have verapamil plasma profiles similar to subject #2. For example in subject #20, the Cmax values are 130.86 and 50.55 ng/mL, for the test and the reference products, respectively, under nonfasting conditions. However, under nonfasting conditions, the plasma verapamil concentrations peaked at 24 hours for the reference product for subject #20, whereas it peaked at 24 hours for subject #2 for the test product. Observations such as these support the conclusion that subject #2 is not an outlier.

2. Verapamil undergoes extensive metabolism in the liver. Intrasubject variability in the rate of metabolism of verapamil to norverapamil may produce different values for norverapamil from hour to hour. Therefore, omitting one single time point and/or setting the value to missing in the statistical analysis is unacceptable. Setting the value to missing for both the test and reference in the plasma concentration-time data set for subject #2 at 24 hours cannot be justified by your argument about verapamil/norverapamil log AUC(0-t) ratios for each analyte for each subject.

3. By using all of the reported data (the actual draw time) and employing the following model,

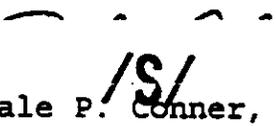
$$Y = \text{seq subj}(\text{seq}) \text{ per trt};$$

The resulting ratios of least-squares means of the log-transformed parameters for verapamil are as following:

LnAUC	1.257
LnAUCinf	1.209
LnCmax	1.243

The ratio for AUC(0-t) parameter exceeds limits of 80-125%.
Therefore, the study is unacceptable.

Sincerely yours,


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

Verapamil HCl ER Tablet
120 mg, 180 mg and 240 mg
ANDA # 75-072
Reviewer: Moheb H. Makary
WP 75072SD.698

Duramed Pharmaceuticals, Inc.
Cincinnati, Ohio
Submission Date:
June 25, 1998

Review of an Amendment

I. Objective:

The firm has replied to the reviewer's deficiency comments made in the review of December 10, 1997 amendment to the pending ANDA #75-072 for Verapamil HCl ER Tablets, 120 mg, 180 mg and 240 mg (letter dated April 7, 1998).

Comment #1

The single-dose fasting bioequivalence study #950277 for the 180 mg strength has been found unacceptable by the division of bioequivalence. The 90% confidence intervals for the LnCmax exceeded the acceptable range of 80-125% for verapamil and norverapamil. The response of the reviewer to the firm's suggestions of formulation proportionality and pooling the studies data is shown on Page 06 of this amendment.

The firm withdraws the 180 mg formulation from ANDA #75-072.

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

The single-dose nonfasting study #950281 for the 240 mg strength has been found unacceptable. The ratios of the test arithmetic means to the reference arithmetic means were not within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax for verapamil under nonfasting conditions. The ratio of least-squares means of the log-transformed AUC(0-t) parameter exceeded the acceptable range of 80-125% for verapamil under nonfasting conditions.

In the previous amendment dated December 10, 1997, the firm proposed to omit subject #2 from the final analysis "since the results obtained for Subject 2 with the reference formulation under fed conditions cannot be computed since at least one critical point is anomalous". In addition, the firm pointed out that "the ratio of least-square means of log-transformed AUC_{0-t} was reported as 125.4%. Based on the application of significant

figures commonly used in the pharmaceutical industry and as outlined in the current USP (General Notices, page 3), this result equals the upper limit of the acceptance range of 125%."

The response of the reviewer to the firm's suggestions is shown on page 07 of this amendment.

In this amendment, for subject #2, the firm indicated that its review of the "Guidance of Statistical Procedures for Bioequivalence Studies" by the Division of Bioequivalence, July 1, 1992, suggests that the proper course should have been to set the single anomalous value to "missing". In the present case, Phoenix (the CRO who conducted the study)'s SOP(AL-G-1520-07) specifies that concentration values that are two times higher or 50% lower than the highest concentration of either the two adjacent concentrations are considered anomalous and are candidates for retesting. Following this SOP, Phoenix analytical reviewer flagged subject #2's 24 hour result for the verapamil (test treatment) to be a potential analytical outlier. This sample was retested in duplicate. The retest results confirmed the initial results of 49.23 ng/mL (retest: 58.13, 62.89 ng/mL). Per SOP, Phoenix reported the median of three values, 58.13 ng/mL.

The firm also indicated that for any given treatment, the profile of verapamil and norverapamil should be consistently parallel, differing only by a constant ratio. The firm speculates that this parallelism arises because norverapamil is the metabolite of verapamil and both are metabolized in the same manner. The firm computed the ratio of log-transformed AUC(0-t) between treatments for each analyte for each subject and then computed the deviation from the arithmetic mean of these ratios for all subjects $(T/R - \text{Mean } T/R) / \text{Mean } T/R * 100$. The results of this analysis are presented on page 08 of this amendment. The results of this analysis showed a strong correlation between ratios for verapamil and norverapamil; only subjects 1, 2 and 16 have a poor correlation. The firm suggested that only subject #2 contains an obvious outlier: the test/reference ratio of the value for verapamil at 24 hours for the test product, which does not correlate well with the ratio of the 24 hour results for norverapamil. Since subject #2's ratio for norverapamil is consistent with the ratio for other subjects, this analysis indicates that the analytical value obtained for the reference product for verapamil is the inconsistent value. Thus, the reference sample is the sample that Phoenix should have retested, not the sample for the test product. Since this sample cannot be retested, the firm excluded subject #2 from the analysis in its previous response. After further examination of the Statistical Guidance and, in review of the reviewer's comments (the Agency letter dated April 7, 1998, i.e., omission of subject #2 from the

final data analysis is not recommended for demonstrating the bioequivalence of the test product), the firm determined that this situation should have been handled by treating the value as missing, per the usual practice when a retest cannot be done due to insufficient or absent sample. The firm indicated that only the reference result for verapamil for subject #2 at 24 hours is anomalous. In order to avoid the bias of comparing a large value for the test and a missing value for the reference, the firm set the value to missing for both the test and reference in the plasma concentration-time data set.

For the pharmacokinetic and statistical analysis of the study, the firm accepted the reviewer's comment that the first-order carryover effects in the original model were not statistically significant. By using the reduced model, i.e., subject, period and treatment and using the entire data set, the firm could not reproduce the LnAUC(0-t) of 1.257 obtained by the reviewer. The firm indicated that a possible cause for this discrepancy was that the reviewer used the nominal draw time data, not the actual draw time data.

Using all reported data for all subjects for verapamil, the firm reported the ratio of LS means for the log transformed AUC(0-t) for test and reference to be 1.2449. Setting the 24 hour concentration for subject #2 to missing (.) gave a LnAUC(0-t) ratio of 1.2401.

The reviewer response

The verapamil and norverapamil plasma concentrations (ng/mL) for subject #2 are shown below:

Time (hr)	Test Fed			Reference Fed		
	Verapamil	Norverapamil	V/N	Verapamil	Norverapamil	V/N
0	0.0	0.0	.	0.0	0.0	.
1	2.11	0.0	.	0.0	0.0	.
2	3.55	0.0	.	0.0	0.0	.
3	10.53	7.54	1.40	4.06	2.80	1.45
4	19.83	12.53	1.58	13.90	11.82	1.18
5	29.55	.	.	20.84	18.73	1.11
6	32.62	29.13	1.12	15.35	22.83	0.67
7	30.93	35.13	0.88	17.88	24.19	0.74
8	25.82	31.48	0.82	21.66	19.95	1.09
9	26.71	36.83	0.72	22.76	31.84	0.71
10	22.87	32.58	0.70	29.80	37.67	0.79
11	19.88	31.68	0.62	20.23	40.22	0.50
12	21.75	20.80	1.05	20.44	32.99	0.62
16	29.42	41.87	0.70	27.79	44.59	0.62

24	58.13	54.03	1.07	26.56	46.37	0.57
36	14.55	31.97	0.45	10.91	24.01	0.45
48	6.10	13.23	1.85	5.71	13.23	0.43

Comments:

1. The firm's argument that the reference result for verapamil for subject #2 at 24 hours is anomalous is unacceptable. In the study some subjects have verapamil plasma profiles similar to subject #2. For example in subject #20, the Cmax values are 130.86 and 50.55 ng/mL, for the test and the reference products, respectively, under nonfasting conditions. However, under nonfasting conditions, the plasma verapamil concentrations peaked at 24 hours for the reference product for subject #20, whereas it peaked at 24 hours for subject #2 for the test product. Observations such as these support the conclusion that subject #2 is not an outlier.

2. Verapamil undergoes extensive metabolism in the liver. There may be intrasubject variability in the rate of metabolism of verapamil to norverapamil. The intrasubject variability may produce different values for norverapamil from hour to hour. Therefore, omitting one single time point and/or setting the value to missing in the statistical analysis is unacceptable. Setting the value to missing for both the test and reference in the plasma concentration-time data set for subject #2 at 24 hours, can not be justified by the firm's argument about the ratio of log AUC(0-t) between treatments for verapamil/norverapamil ratios for each analyte for each subject.

3. By using all of the reported data (the actual draw time) and employing the following model,

$$Y = \text{seq subj}(\text{seq}) \text{ per trt};$$

the resulting ratios of least-squares means of the log-transformed parameters for verapamil are as following:

LnAUC	1.257
LnAUCinf	1.209
LnCmax	1.243

The ratio for AUC(0-t) parameter exceeds limits of 80-125%.

Therefore, the study is unacceptable

Reply to Comment #2

The firm's response to the comment is unacceptable.

II. Recommendation:

The single-dose post-prandial bioequivalence study #950281, conducted by Duramed Pharmaceuticals, Inc., on its Verapamil HCl 240 mg ER tablet, lot #950301, comparing it to Isoptin[®] SR 240 mg tablet, manufactured by Knoll Pharmaceuticals, has been found unacceptable by the Division of Bioequivalence for the reasons given in comments 1-3.

= The firm should be informed of the comments and recommendation.

/S/

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

Date: 10-15-98

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

As of 10/15/98

Date: 10/13/98

Concur: */S/*
Dale P. Corner, Pharm.D.
Director
Division of Bioequivalence

Date: 10/16/98

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BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-072

APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Verapamil HCl ER Tablets, 120 mg, 180 mg and 240 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You propose that the reference result for verapamil for subject #2 at 24 hours is anomalous. This argument is unacceptable for the following reasons. In the single-dose post-prandial bioequivalence study #950281, some subjects have verapamil plasma profiles similar to subject #2. For example in subject #20, the Cmax values are 130.86 and 50.55 ng/mL, for the test and the reference products, respectively, under nonfasting conditions. However, under nonfasting conditions, the plasma verapamil concentrations peaked at 24 hours for the reference product for subject #20, whereas it peaked at 24 hours for subject #2 for the test product. Observations such as these support the conclusion that subject #2 is not an outlier.

2. Verapamil undergoes extensive metabolism in the liver. Intrasubject variability in the rate of metabolism of verapamil to norverapamil may produce different values for norverapamil from hour to hour. Therefore, omitting one single time point and/or setting the value to missing in the statistical analysis is unacceptable. Setting the value to missing for both the test and reference in the plasma concentration-time data set for subject #2 at 24 hours cannot be justified by your argument about verapamil/norverapamil log AUC(0-t) ratios for each analyte for each subject.

3. By using all of the reported data (the actual draw time) and employing the following model,

$$Y = \text{seq subj}(\text{seq}) \text{ per trt};$$

The resulting ratios of least-squares means of the log-transformed parameters for verapamil are as following:

LnAUC	1.257
LnAUCinf	1.209
LnCmax	1.243

The ratio for AUC(0-t) parameter exceeds limits of 80-125%.
Therefore, the study is unacceptable.

Sincerely yours,

/s/

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



Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

The Art of Leadership...
The Science of Change

June 25, 1998

*NAI
"Bio Response"
[Signature]
7/13/98*

Dale Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC to

**Re: ANDA 75-072
Verapamil Hydrochloride Extended-Release Tablets USP,
120 mg, 180 mg and 240 mg**

Subject: BIOEQUIVALENCE AMENDMENT

Dear Dr. Conner:

Reference is made to your correspondence dated April 7, 1998 concerning two (2) review comments on bioequivalence studies in our pending Abbreviated New Drug Application 75-072 for Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg.

We have noted the comments cited and are amending the application, having responded fully to all of the comments. For each item we first restate the comment then present our response.

This **Bioequivalence Amendment** includes two (2) copies, an archival (blue) copy and a review (orange) copy.

If you have any questions, please feel free to contact Mr. Ken Phelps at (513) 458-7325, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Encl. FDA Form 356H

Desk copy: L Sanchez (Fax copy for reviewer)

RECEIVED

JUN 26 1998

GENERIC DRUGS

*Phelps
6/29/98*

Verapamil Hydrochloride ER Tablets
ANDA # 75-072: 120, 180 & 240 mg
Reviewer: Hoainhon Nguyen
WP #75072a.d97

Duramed Pharmaceuticals
Cincinnati, OH
Submission Date:
December 10, 1997

Review of a Study Amendment

The firm has submitted a study amendment in response to the Division of Bioequivalence's Deficiency Comments issued in the letter dated August 18, 1997. The Deficiency Comments, the firm's summarized Responses and the DBE's Comments on the firm's Responses are given below.

Deficiency Comments:

- 1. *For the single-dose bioequivalence fasting study #050277 conducted on Verapamil HCl ER tablet, 180mg, the 90% confidence intervals for Cmax exceed the acceptable range of 80-125% for log-transformed data for both verapamil and norverapamil. Therefore, this study is unacceptable.*
- 2. *For the single-dose bioequivalence study #050281, conducted on Verapamil HCl Tablet, 240 mg under fasting and non-fasting conditions, the ratios of the test arithmetic means to the reference arithmetic means are not within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf or Cmax for verapamil under non-fasting conditions. The ratio of least-squares means of the log-transformed AUC(0-t) parameter exceeds the acceptable range of 80-125% for verapamil under non-fasting conditions. Therefore, this study is also unacceptable.*
- 3. *The multiple-dose bioequivalence study #050282, conducted on Verapamil HCl ER tablet, 240 mg, is incomplete. A single oral 240 mg dose of verapamil Hydrochloride was administered q24h for a total of six doses. You reported AUC(0-T) calculations and Cmax concentrations for each subject for both verapamil and norverapamil from 144 to 168 hours instead of from 120 to 144 hours. Please explain this discrepancy; and submit the dosing and sampling dates for each subject in the study.*

4. *Submission of dissolution testing results for each dosage unit, test and reference, (i.e., for each of the 12 whole and half tablets), for each strength, in addition to the coefficient of variation, mean and range for the dissolution at each time point, are needed for proper evaluation.*
5. *On the remaining studies, #Q41081 and #Q50257, we have no further questions. However, the dissolution data remains incomplete. (See comment 4)"*

Firm's Response:

1. The firm has proposed to pool the results of all three single-dose, fasting bioequivalence studies on the 120-mg, 180-mg and 240-mg dosage strengths of the test product. The firm argues that *"This pooled analysis (attached) is reasonable since the 120-, 180- and 240 mg dosage strengths are simply proportional tablet weights of a common granulation"* and *"the dosage strength is simply the result of compressing different tablet weights."*

2. The firm has proposed to omit Subject #2 from the final analysis *"since the results obtained for Subject 2 with the reference formulation under fed conditions cannot be computed since at least one critical point is anomalous"*. In addition, the firm pointed out that *"the ratio of least-square means of log-transformed AUC_{0-t} was reported as 125.4%. Based on the application of significant figures commonly used in the pharmaceutical industry and as outlined in the current USP (General Notices, page 3), this result equals the upper limit of the acceptance range of 125%."*

3. *"The reviewer is correct, the final dose, Dose 6, was given at 120 hours, not 144 hours as stated in the report submitted in the original ANDA. The error was caused at Phoenix (the CRO) during the data entry of the information from the plasma collection tubes; the tubes were labeled with day and hour and the analyst incorrectly converted these times into the hour from dosing."*

All the time-points presented in the original report are off-scale by 24 hours. However, the error does not affect the statistical analyses, and the representation and interpretation of the pharmacokinetic parameters and the conclusion of the

study remain unchanged. The firm has provided the revised report of the study using correct time points.

4. The firm has submitted the dissolution data for the half-tablets for the 180 and 240 mg strengths of both the test and reference products as requested (NOTE: The 120 mg strength of both the test and reference products is not scored). The dissolution data for the whole tablets for both the test and reference products were submitted and summarized in the previous review (dated August 4, 1997). The additional dissolution results are summarized below.

Dissolution Results:

Drug (Generic Name): Verapamil HCl ER Tablets Firm: Duramed
 Dose Strength: 120, 180 & 240 mg ANDA # 75-072
 Submission Date: December 10, 1997

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket Paddle X RPM 50 No. Units Tested: 12

Medium: Acid Stage: SGF without enzyme; Volume: 900 mL

Buffer Stage: SIF without enzyme; Volume: 900 mL

Reference Drug: (Manuf.) Isoptin SR Tablets (Knoll)

Assay Methodology: Not given

II. Results of In-Vitro Dissolution Testing: Half-Tablets

Sampling Times (hr)	Test Product			Reference Product		
	Mean % Dissolved	Range	(CV%)	Mean % Dissolved	Range	(CV%)
<u>1</u>	<u>16.5</u>		<u>(5.8)</u>	<u>13.3</u>		<u>(6.0)</u>
<u>2</u>	<u>27.0</u>		<u>(6.0)</u>	<u>22.8</u>		<u>(6.6)</u>
<u>3.5</u>	<u>51.4</u>		<u>(6.9)</u>	<u>49.5</u>		<u>(7.3)</u>
<u>5</u>	<u>74.3</u>		<u>(4.2)</u>	<u>73.3</u>		<u>(4.6)</u>
<u>8</u>	<u>99.6</u>		<u>(2.1)</u>	<u>99.3</u>		<u>(1.9)</u>

Sampling Times (hr)	Test Product			Reference Product		
	Lot #	Strength (mg)		Lot #	Strength (mg)	
	960701	180		21290026	180	
	Mean %	Range	(CV%)	Mean %	Range	(CV%)
	Dissolved			Dissolved		
1	17.4		(4.6)	17.1		(6.6)
2	28.3		(5.3)	28.2		(6.4)
3.5	56.0		(4.0)	57.5		(2.2)
5	79.9		(2.3)	81.4		(3.2)
8	99.3		(0.9)	99.3		(1.3)

Current Specifications:

5. See the Firm's Response #4 above.

DBE's Comments on Firm's Responses:

1. Even though the formulations are simply proportional tablet weights of a common granulation, the 120 mg, 180 mg and 240 mg strengths of the test product are considered as different tablet products due to the difference in the tablet compression. Although only single-dose, fasting studies are required for the lower strengths and the steady-state and non-fasting studies are waived, these required studies are pivotal in demonstrating that different tablet compression does not affect the *in vivo* extended-release performance of each strength of the test product as compared with the respective strengths of the reference listed drug product. Each single-dose study must stand on its own in demonstrating the bioequivalency of each lower strength and can not be pooled. The proposal by the firm for pooling all the fasting studies is therefore unacceptable.

It should be noted that, in contrary, for extended-release capsule formulation marketed in multiple strengths, single-dose fasting bioequivalence studies may be waived for the lower strengths on the basis of acceptable dissolution profiles and the identical beads or pellets contained in the capsule formulations since other

differences between strengths, such as tablet compression, are absent.

2. The firm has not provided a scientific evidence or clinical explanation for Subject #2's pharmacokinetic profile which appears "anomalous". The interchangeability between the test and reference products would be of concern for individual patients such as Subject #2 due to the significant difference between the test and reference products' pharmacokinetic profiles, as pointed out by the firm. Omission of Subject #2 from the final data analyses is therefore not recommended for demonstrating the bioequivalency of the test product. Please refer to Guidance of Statistical Procedures for Bioequivalence Studies by the Division of Bioequivalence, issued July 1, 1992, for further discussion on "Outlier Consideration".

In addition, as it should have been mentioned in the agency's last deficiency letter concerning the ratio of log-transformed mean AUC_{0-t} being outside the [0.80-1.25] limit, the ratio the reviewer referred to is actually 1.257, instead of 1.254, as calculated by the firm. The reviewer statistically re-analyzed the data since the first-order carryover effects in the original models for the analyzed parameters were not significant ($p=0.9, 0.77$ and 0.82 for $LnAUC_{0-t}$, $LnAUC_{inf}$ and LnC_{MAX} , respectively). After excluding the carryover effects from the ANOVA models and recalculating the 90% confidence intervals for these PK parameters based on the new models, the reviewer arrived at the above ratio (1.257) for log-transformed AUC_{0-t} .

3. The firm's responses to this Deficiency comment are adequate and acceptable. The results for the bioequivalence study #950282, as summarized in the previous review, are acceptable.

4 & 5. The dissolution data as submitted are acceptable.

DBE's Overall Recommendations:

1. The firm's response addressing the Deficiency Comment#1 has been found unacceptable for the reason cited in DBE's Comment on the response above. The single-dose bioequivalence fasting study #950277 conducted by Duramed

Pharmaceuticals on its Verapamil HCl ER tablet, 180mg, Lot No. 960701S, comparing it to Isoptin® SR 180 mg Tablet, manufactured by Knoll, is therefore considered unacceptable.

2. The firm's response addressing the Deficiency Comment #2 has also been found unacceptable for the reason cited in DBE's Comment on the corresponding response above. The single-dose bioequivalence post-prandial study #950281 conducted by Duramed Pharmaceuticals on its Verapamil HCl ER tablet, 240mg, Lot No. 950301, comparing it to Isoptin® SR 240 mg Tablet, manufactured by Knoll, is therefore also considered unacceptable.

3. The multiple-dose steady-state bioequivalence study #950282 conducted by Duramed on its Verapamil HCl 240 mg ER Tablets, Lot No. 950301, comparing it to Isoptin® 240 mg SR Tablets, manufactured by Knoll, has been found acceptable by the Division of Bioequivalence. The test product is deemed bioequivalent to the reference listed drug product under steady-state conditions.

4. The dissolution testing for the test and reference product, as whole and half tablets, is acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of SGF without enzyme at 37°C for the first hour, and in 900 ml of SIF without enzyme at 37°C for 2 to 8 hours, both stages using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following tentative specifications:

Hoi ²¹ Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/

3/31/98

Concur:

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

Date: 4/2/98

Attachments: 0 pages

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-072

APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: Verapamil HCl ER Tablets, 120 mg, 180 mg and 240 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your response to the division's deficiency comment #1 (concerning the single-dose fasting bio study #950277 for the 180 mg strength of the test product) has been found **unacceptable** for the following reasons. Even though the formulations are simply proportional tablet weights of a common granulation, the 120 mg, 180 mg and 240 mg strengths of the test product are considered as **different tablet products** due to the difference in the tablet compression. Although only single-dose, fasting studies are required for the lower strengths and the steady-state and non-fasting studies are waived, these required studies are pivotal in demonstrating that different tablet compression does not affect the *in vivo* extended-release performance of each strength of the test product as compared with the respective strengths of the reference listed drug product. **Each single-dose study must stand on its own in demonstrating the bioequivalency of each lower strength and can not be pooled.** The proposal by you for pooling all the fasting studies is therefore **unacceptable**.

2. Your response to the division's deficiency comment #2 (concerning the single-dose non-fasting bio study #950281 for the 240 mg strength of the test product) has been found **unacceptable** for the following reasons. You have not provided scientific evidence or a clinical explanation for Subject #2's pharmacokinetic profile which appears "anomalous". The interchangeability between the test and reference products would be of concern for individual patients such as Subject #2 due to the significant difference between the test and reference products' pharmacokinetic profiles, as pointed out by you. Omission of Subject #2 from the final data analyses is therefore not recommendable for demonstrating the bioequivalency of the test product. Please refer to Guidance of Statistical Procedures for Bioequivalence Studies by the Division of Bioequivalence, issued July 1, 1992, for further discussion on "Outlier Consideration".

In addition, as it should have been mentioned in the agency's last deficiency letter concerning the ratio of log-transformed mean AUC_{0-t} being outside the [0.80-1.25] limit, the ratio the reviewer referred to is actually 1.257, instead of 1.254, as calculated by the firm. The reviewer statistically re-analyzed the data since the first-order carryover effects in the original models for the analyzed parameters were nonsignificant ($p=0.9$, 0.77 and 0.82 for $\ln AUC_{0-t}$, $\ln AUC_{1hr}$ and $\ln C_{MAX}$, respectively). After excluding the carryover effects from the ANOVA models and recalculating the 90% confidence intervals for these PK parameters based on the new models, the reviewer arrived at the above ratio (1.257) for log-transformed AUC_{0-t} .

Sincerely yours,

/s/

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

APR 7 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-072

APPLICANT: Duramed Pharmaceuticals

DRUG PRODUCT: Verapamil HCl ER Tablets, 120 mg, 180 mg and 240 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your response to the division's deficiency comment #1 (concerning the single-dose fasting bio study #950277 for the 180 mg strength of the test product) has been found **unacceptable** for the following reasons. Even though the formulations are simply proportional tablet weights of a common granulation, the 120 mg, 180 mg and 240 mg strengths of the test product are considered as **different tablet products** due to the difference in the tablet compression. Although only single-dose, fasting studies are required for the lower strengths and the steady-state and non-fasting studies are waived, these required studies are pivotal in demonstrating that different tablet compression does not affect the *in vivo* extended-release performance of each strength of the test product as compared with the respective strengths of the reference listed drug product. **Each single-dose study must stand on its own in demonstrating the bioequivalency of each lower strength and can not be pooled.** The proposal by you for pooling all the fasting studies is therefore **unacceptable**.

2. Your response to the division's deficiency comment #2 (concerning the single-dose non-fasting bio study #950281 for the 240 mg strength of the test product) has been found **unacceptable** for the following reasons. You have not provided scientific evidence or a clinical explanation for Subject #2's pharmacokinetic profile which appears "anomalous". The interchangeability between the test and reference products would be of concern for individual patients such as Subject #2 due to the significant difference between the test and reference products' pharmacokinetic profiles, as pointed out by you. Omission of Subject #2 from the final data analyses is therefore not recommendable for demonstrating the bioequivalency of the test product. Please refer to Guidance of Statistical Procedures for Bioequivalence Studies by the Division of Bioequivalence, issued July 1, 1992, for further discussion on "Outlier Consideration".

In addition, as it should have been mentioned in the agency's last deficiency letter concerning the ratio of log-transformed mean AUC_{0-t} being outside the [0.80-1.25] limit, the ratio the reviewer referred to is actually 1.257, instead of 1.254, as calculated by the firm. The reviewer statistically re-analyzed the data since the first-order carryover effects in the original models for the analyzed parameters were nonsignificant ($p=0.9$, 0.77 and 0.82 for $\text{Ln}AUC_{0-t}$, $\text{Ln}AUC_{inf}$ and $\text{Ln}C_{MAX}$, respectively). After excluding the carryover effects from the ANOVA models and recalculating the 90% confidence intervals for these PK parameters based on the new models, the reviewer arrived at the above ratio (1.257) for log-transformed AUC_{0-t} .

Sincerely yours,

/S/

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



BIOAVAILABILITY

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

*The Art of Leadership...
The Science of Change*

December 10, 1997

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
AB

RE: **ANDA 75-072 Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg**

Subject: **BIOEQUIVALENCE AMENDMENT**

Dear Mr. Sporn:

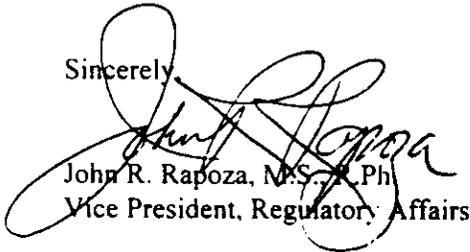
Reference is made to your correspondence dated August 18, 1997 concerning review comments on bioequivalence studies in our Abbreviated New Drug Application 75-072 for Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg.

We have noted the comments cited and are amending the application, having responded fully to all of the comments. For each item we first restate the comment then present our response.

This **Bioequivalence Amendment** includes two (2) copies, an archival (blue) copy and a review (orange) copy.

If you have any questions, please feel free to contact Mr. Ken Phelps at (513) 731-9900, or the undersigned at (513) 458-7274.

Sincerely,


John R. Rapoza, M.S., Ph.D.
Vice President, Regulatory Affairs

cc: E.T. Arington (letter only)
K. Patel

RECEIVED

DEC 11 1997

GENERIC DRUGS



The Art of Leadership...
The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

December 17, 1997

RECEIVED

M/AB

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA 75-072 Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg**

Subject: **BIOEQUIVALENCE AMENDMENT**

Dear Mr. Sporn:

Reference is made to our amendment dated December 10, 1997 regarding our response to your comments on bioequivalence studies in our Abbreviated New Drug Application 75-072 for Verapamil HCl ER Tablets, USP, 120 mg, 180 mg, 240 mg.

Pages 236-238 of the amendment contain comparative tablet dissolution tables. The footnote on page 235 of the amendment references the April 4, 1997 amendment to the application as the original source of the tables. The tables that were submitted in the December 10, 1997 amendment are for core tablet comparative dissolution instead of reference product dissolution; these tables were submitted in our October 24, 1997 amendment. The correct comparative dissolution tables which were originally submitted April 4, 1997, are now included as Tables 3a, 4a and 5a and are paginated as 236a, 237a and 238a in reference to the December 10, 1997 amendment. To aide the reviewer, we have revised page 235 of the amendment to include reference to these Tables; it is numbered as page 235a.

We apologize for any inconvenience this oversight may have caused.

This **Bioequivalence Amendment** includes two (2) copies, an archival (blue) copy and a review (orange) copy.

If you have any questions, please feel free to contact Mr. Ken Phelps at (513) 731-9900, or the undersigned at (513) 458-7274.

Sincerely,

Annette Carlingham / for
John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

cc: K. Patel

RECEIVED

DEC 18 1997

GENERIC DRUGS

2.1
P. Keating
AUG 18 1997

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213

Dear Sir:

Reference is made to the Abbreviated New Drug Application and the amendments submitted on June 2 and 13, 1997, for Verapamil Hydrochloride Extended Release Tablets, 120mg, 180mg and 240mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. For the single-dose bioequivalence fasting study #950277 conducted on Verapamil HCl ER tablet, 180mg, the 90% confidence intervals for C_{max} exceed the acceptable range of 80-125% for log-transformed data for both verapamil and norverapamil. Therefore, this study is unacceptable.
2. For the single-dose bioequivalence study #950281, conducted on Verapamil HCl Tablet, 240 mg under fasting and non-fasting conditions, the ratios of the test arithmetic means to the reference arithmetic means are not within the acceptable range of 0.8-1.2 for $AUC(0-t)$, AUC_{inf} or C_{max} for verapamil under non-fasting conditions. The ratio of least-squares means of the log-transformed $AUC(0-t)$ parameter exceeds the acceptable range of 80-125% for verapamil under non-fasting conditions. Therefore, this study is also unacceptable.
3. The multiple-dose bioequivalence study #950282, conducted on Verapamil HCl ER tablet, 240 mg, is incomplete. A single oral 240 mg dose of verapamil Hydrochloride was administered q24h for a total of six doses. You reported $AUC(0-T)$ calculations and C_{max} concentrations for each subject for both verapamil and norverapamil from 144 to 168 hours instead of from 120 to 144 hours. Please explain this discrepancy; and submit the dosing and sampling dates for each subject in the study.
4. Submission of dissolution testing results for each dosage unit, test and reference, (i.e., for each of the 12 whole and half tablets), for each strength, in addition to the coefficient of variation, mean and range for the dissolution at each time point, are needed for proper evaluation.

5. On the remaining studies, #941081 and #950257, we have no further questions. However, the dissolution data remains incomplete. (See comment 4)

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

[^]
/S/

fr Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Verapamil HCl ER Tablet
120 mg, 180 mg and 240 mg
ANDA # 75-072
Reviewer: Moheb H. Makary
WP 75072SD.297

Duramed Pharmaceuticals, Inc.
Cincinnati, Ohio
Submission Date:
February 10, 1997
June 2, 1997
June 13, 1997

Review of Bioequivalence Studies and Dissolution Data

I. Objective:

The firm submitted the data and results from five (5) *In Vivo* Bioequivalence Studies, and the *In Vitro* dissolution data for its Verapamil HCl Extended Release Tablets, USP, 120mg, 180 mg and 240 mg.

The five *in vivo* bioequivalence studies titled:

1. "Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Hallmark and Knoll (Isoptin® SR) 240 mg Verapamil HCl Sustained-Release Tablets in Healthy Adult Males Under Fasting Conditions" - Protocol No. 941081.
2. "Comparative, Randomized, Steady-State, 2-Way Crossover Bioavailability Study of Hallmark and Knoll (Isoptin® SR) 240 mg Verapamil HCl Sustained-Release Tablets in Healthy Adult Males Under Fasting Conditions" - Protocol No. 950282.
3. "Comparative, Randomized, Single-Dose, 3-Way Crossover Bioavailability Study of Hallmark and Knoll (Isoptin® SR) 240 mg Verapamil HCl Sustained-Release Tablets in Healthy Adult Males Under Nonfasting and Fasting Conditions" - Protocol No. 950281.
4. "Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Hallmark and Knoll (Isoptin® SR) 180 mg Verapamil HCl Sustained-Release Tablets in Healthy Adult Males Under Fasting Conditions" - Protocol No. 950277.
5. "Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Hallmark and Knoll (Isoptin® SR) 120 mg Verapamil HCl Sustained-Release Tablets in Healthy Adult Males Under Fasting Conditions Following Administration of a 240 mg Dose" - Protocol No. 950257.

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 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.

III. Study #950257 For Single-Dose, Two-Way Crossover On Verapamil HCl Extended Release Tablets, 120 mg, Under Fasting Conditions:

Objective: The objective of the study was to compare the bioavailability of verapamil-ER tablets manufactured by Duramed Pharmaceuticals, Inc., with that of Knoll product (Isoptin^R SR), following an oral administration of a single 240 mg dose (2x120 mg tablets) of each product under fasting conditions.

Study site: Phoenix International
Cincinnati, OH.

Sponsor: Duramed Pharmaceuticals, Inc.

Study design: Single-dose, randomized, 2-way crossover, open-label, under fasting conditions.

Subjects: Forty five (45) healthy adult male subjects were enrolled in two groups, and 37 completed the study. Statistical analysis was performed only on the data from subjects who completed the crossover. The dosing dates for this study were as following:

Phase I	Phase II
Group A July 19, 1996	August 2, 1996
Group B August 9, 1996	August 23, 1996

Selection criteria: The subjects were between 18 to 45 years of age. All subjects were within $\pm 15\%$ 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, ECG 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. Subjects who, through completion of this study, would have donated in excess of 500 mL of blood in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 ML in one year.

Restrictions: Subjects were instructed not to take any drugs for 7 days prior to and during the course of the study. In addition, no concomitant medication was permitted during the study period. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine-containing products for 24 hours prior to, and throughout the period of sample collection.

Dose and Treatments: Treatment A: 2x120 mg verapamil HCl ER tablets (Duramed), lot #960702S, batch size Tablets, potency 100.7%, content uniformity 98.3% (CV=1.0%), administered following an overnight fast. Treatment B: 2x120 mg Isoptin®SR tablets (Knoll), lot #20900016, Exp. 7/98, potency 98.5%, content uniformity 98.8%

(CV=1.1%), administered following an overnight fast.

Washout period: Two weeks

Food and fluid intake:

Subjects fasted for at least 10 hours prior to dosing. Lunch was served four hours after dosing. Dinner was served 9 hours after dosing. Water was not allowed from two hours before the dose and 4 hours after the dose, 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, 15, 14, 16, 24, 36, 48 and 72 hours after dosing. Plasma samples were immediately frozen.

Subject welfare: Vital signs were measured before dosing and at approximately 10 minutes before the scheduled blood draws at 3, 6, 9, 12 and 24 hours after dosing. 12-Lead EKGs were recorded for each subject within 1 hour before dosing and within 20 minutes before the 3, 6, 9, 12 and 24-hour blood samples following drug administration. Subjects laid down from at least 5 minutes before until completion of EKG. The EKG electrodes remained in place until after the 24-hour post-dose EKGs were performed.

Assay Methodology:

Determination of verapamil and norverapamil plasma concentrations were performed by _____ with a _____ detection and _____ as an internal standard.

Sensitivity: The limit of quantitation was 2.0 ng/mL for verapamil and norverapamil.

Linearity: The assay was linear over the concentration range of 2.5 to 500.0 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.

Recovery: The mean recovery is 80.5% for verapamil and 89.0% for norverapamil.

**Interday precision
and accuracy:**

Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from 6.6% to 8.9% and 4.6% to 7.4% for verapamil and norverapamil, respectively. Accuracy ranged from 94.8% to 98.9% and 97.3% to 101.7% for verapamil and norverapamil, respectively.

**Intraday precision
and accuracy:**

Intraday precision were calculated using six spiked samples at each of four concentrations 2, 5, 201 and 402 ng/mL assayed on the same day. The coefficients of variation ranged from 1.9% to 4.5% and 1.6% to 6.2% for verapamil and norverapamil, respectively. Accuracy ranged from 94.8% to 97.7% and from 89.7% to 98.5% for verapamil and norverapamil, respectively.

Stability:

Freeze-Thaw Stability: Verapamil and norverapamil were spiked into plasma at low and high concentrations. These samples were subjected to seven freeze-thaw cycles. Verapamil and norverapamil samples were found to be stable through seven freeze/thaw cycles. **Short Term Stability:** Samples were set at room temperature up to 8 hours. The samples did not show significant degradation when stored at room temperature up to 8 hours. **Long term stability:** stability was assessed by quantitation of spiked plasma samples which were frozen for 108 days at -22°C. The results showed no degradation of verapamil or norverapamil for a period up to 108 days.

Statistical Analysis:

Statistical analysis was performed on verapamil and norverapamil data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic 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 two separate groups. An analysis of variance was performed to assess the group effect and determine the pool ability of the two groups. A model with terms for groups, sequences, subjects within the group by sequence

interaction, treatments and periods was performed. No statistically significant group effects were observed for the pharmacokinetic parameters by using the above model.

IV. In Vivo Results:

Thirty-seven (37) subjects successfully completed both phases of the clinical portion of the study. The clinical study was conducted in two groups. Of the 30 healthy adult male subjects initially enrolled in the study (group A), three subjects (subjects #1, 6 and 10) were withdrawn from the study approximately 3 hours after period I dosing (test product) due to high PR intervals in the EKG, and four additional subjects (subjects #5, 13, 26 and 31) withdrew for personal reasons or were withdrawn for failure to comply with the protocol. An additional 15 subjects (group B) were recruited, one (subject #44) of whom withdrew for personal reasons. As mention above, three subjects (subjects #1, 6 and 10) were withdrawn from the study approximately 3 hours after period I dosing (test product) due to high PR intervals in the EKG. Additionally, ten adverse events were reported to be probably or possibly drug related and eleven events were reported to be not drug related.

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

Table I

Mean Plasma Verapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Verapamil HCl ER (2x120 mg Tablets) under Fasting Conditions
(N=37)

(hr)	Test Formulation Duramed Lot#960702S ng/mL (CV%)	Reference Formulation Knoll Lot#20900016 ng/mL (CV%)
0	0.00	0.00
1.0	6.879 (107.1)	8.873 (98.7)
2.0	34.011 (84.5)	41.294 (94.7)
3.0	75.766 (73.3)	65.298 (82.5)
4.0	98.008 (69.8)	82.431 (89.8)

5.0	109.305 (57.5)	96.017 (66.8)
6.0	97.799 (53.0)	99.802 (56.6)
7.0	80.604 (50.1)	89.722 (47.0)
8.0	67.104 (48.7)	75.866 (46.1)
9.0	55.421 (48.7)	65.224 (49.9)
10	51.908 (44.4)	60.927 (61.3)
11	41.617 (41.8)	49.867 (60.2)
12	36.614 (44.8)	42.603 (54.6)
13	31.303 (48.5)	36.739 (54.7)
14	26.673 (49.4)	32.179 (53.4)
16	21.858 (52.9)	25.546 (59.5)
24	14.395 (60.7)	15.226 (60.1)
36	4.898 (72.1)	5.038 (71.2)
48	1.988 (119.1)	1.941 (113.3)
72	0.127 (412.8)	0.197 (342.3)

AUC(0-t) (ng.hr/mL)	1145.4 (45.1)	1213.8 (48.1)
AUCinf (ng.hr/mL)	1198.5 (43.3)	1258.7 (46.6)
Cmax (ng/mL)	121.8 (53.1)	118.2 (57.8)
Tmax (hr)	5.20	6.35
Kel (1/hr)	0.076	0.079
T1/2 (hr)	9.99	9.35
LnAUC(0-t)		87.6-106.1%
LnAUCinf		88.4-106.7%
LnCmax		88.1-122.3%

1. For Verapamil, the least squares means for AUC(0-t), AUCinf and Cmax values were 3.8%, 2.8% and 3.8% lower and higher, respectively, for the test product than for the reference product. The differences were 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 same as those submitted by the firm.

2. The Verapamil plasma levels peaked at 5 and 6 hours for the test and the reference products, respectively, following their administration under fasting conditions.

3. The Division of Biometrics recommended using the following model:

$$Y = \text{SEQ SUBJ}(\text{SEQ}) \text{ PER TRT}; \quad (\text{whereas period} = 4)$$

Analysis of variance was performed by the reviewer using the above model, the resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax were as following:

Verapamil

LnAUC(0-t)	87.4-106.2%
LnAUCinf	88.3-106.9%
LnCmax	87.9-122.9%

Norverapamil

LnAUC(0-t)	88.1-105.0%
LnAUCinf	88.7-104.7%
LnCmax	85.7-111.4%

- All confidence intervals remained within the acceptable 80-125% range.

Table II

Mean Plasma Norverapamil Concentrations and Pharmacokinetic
Parameters Following an Oral Dose of 240 Verapamil HCl
ER (2x120 mg Tablets) under Fasting Conditions
(N=37)

Time (hr)	Test Formulation Duramed Lot#960702S ng/mL (CV%)	Reference Formulation Knoll Lot#20900016 ng/mL (CV%)
0	0.00	0.00
1.0	5.827 (99.3)	6.904 (87.7)
2.0	30.015 (90.4)	30.726 (76.5)
3.0	62.655 (70.6)	53.904 (68.8)
4.0	86.175 (59.3)	72.324 (65.7)
5.0	102.116 (50.1)	88.065 (54.4)
6.0	102.164 (45.0)	97.319 (48.2)
7.0	99.895 (42.9)	99.016 (41.6)
8.0	92.579 (40.8)	97.211 (41.8)
9.0	83.721 (37.2)	88.059 (39.6)
10	77.158 (33.2)	84.957 (39.3)
11	69.055 (30.2)	76.826 (41.9)
12	62.716 (29.4)	68.629 (38.3)
13	57.701 (27.9)	64.943 (38.2)

14	51.782 (28.4)	60.216 (35.3)
16	44.222 (30.6)	49.783 (36.1)
24	28.470 (35.8)	30.676 (39.8)
36	10.553 (52.9)	11.522 (47.8)
48	5.085 (65.7)	5.318 (54.2)
72	0.546 (207.3)	0.619 (178.4)

AUC(0-t) (ng.hr/mL)	1699.1 (30.0)	1784.2 (31.7)	
AUCinf (ng.hr/mL)	1755.8 (29.2)	1839.2 (31.0)	
Cmax (ng/mL)	112.8 (42.6)	115.3 (42.0)	
Tmax (hr)	6.81	7.66	
Kel(1/hr)	0.076	0.079	
T1/2(hr)	9.73	10.05	
LnAUC(0-t)			88.2-104.9%
LnAUCinf			88.8-104.6%
LnCmax			85.9-111.2%

1. For norverapamil, the least squares means for AUC(0-t), AUCinf and Cmax values were 3.2%, 3.6% and 2.3% lower, respectively, for the test product than for the reference product. The differences were 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 same as those submitted by the firm.

2. The norverapamil plasma levels peaked at 6 and 7 hours for the test and the reference products, respectively, following their administration under fasting conditions.

V. Study #950277 For Single-Dose, Two-Way Crossover On Verapamil HCl Extended Release Tablets, 180 mg, Under Fasting Conditions:

Objective: The objective of the study was to compare the bioavailability of verapamil-ER tablets manufactured by Duramed Pharmaceuticals, Inc., with that of Knoll product (Isoptin^R SR), following an oral administration of a single 180 mg dose (1x180 mg tablet) of each product under fasting conditions.

Study site: -----, ---

Sponsor: Duramed Pharmaceuticals, Inc.

Study design: Single-dose, randomized, 2-way crossover, open-label, under fasting conditions.

Dosing date: July 13 and 27, 1996.

Subjects: Thirty-six (36) healthy adult male subjects enrolled, and 35 completed the study. Subject #20 withdrew from the study 2 days after period I dosing for personal reasons. Selection and exclusion criteria were the same as study #950257 above.

Dose and

Treatments: Treatment A: 1x180 mg verapamil HCl ER tablet (Duramed), lot #960701S, batch size .ablets, potency 100.2%, content uniformity 99.1% (CV=0.9%), administered following an overnight fast.
Treatment B: 1x180 mg Isoptin®SR tablet (Knoll), lot #21290026, Exp. 8/98, potency 102.8% content uniformity 100.1% (CV=1.2%), administered following an overnight fast.

Washout period: Two weeks

Subject welfare: Same as study #950257 above.

Assay Methodology: Same as study #950257 above.

VI. In Vivo Results:

Thirty-six (36) subjects enrolled and thirty-five (35) successfully completed both phases of the clinical portion of the study. Subject #20 withdrew from the study 2 days after period I dosing for personal reasons. Seven adverse events [headache (5), lightheaded (1) and heart palpitations (1)] were reported to be probably or possibly drug related.

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

Table III

Mean Plasma Verapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 180 Verapamil HCl ER (1x180 mg Tablet) under Fasting Conditions
(N=35)

Time (hr)	Test Formulation Duramed Lot#960701S ng/mL (CV%)	Reference Formulation (Isoptin®) Lot#21290026 ng/mL (CV%)
0	0.00	0.00
1.0	2.882 (166.2)	3.712 (154.1)
2.0	17.985 (113.9)	18.595 (115.9)
3.0	50.460 (84.8)	35.995 (85.8)
4.0	67.389 (70.5)	49.291 (76.9)
5.0	84.986 (60.1)	68.930 (71.9)
6.0	78.229 (49.3)	70.841 (67.1)
7.0	62.375 (52.3)	65.425 (61.5)
8.0	48.314 (49.5)	56.147 (59.2)
9.0	41.292 (51.8)	47.108 (58.6)
10	33.121 (46.9)	43.145 (56.6)
11	29.422 (45.4)	38.115 (53.8)
12	26.183 (48.0)	33.637 (54.6)

13	22.728 (51.0)	28.152 (48.9)
14	18.805 (47.7)	23.807 (45.7)
16	14.671 (51.8)	17.432 (48.1)
24	8.945 (53.9)	11.089 (60.4)
36	3.009 (59.3)	4.022 (73.6)
48	0.982 (146.7)	1.167 (150.5)
72	0.00	0.00

AUC(0-t) (ng.hr/mL)	783.1 (41.4)	832.9 (46.8)	
AUCinf(ng.hr/mL)	825.7 (41.3)	910.3 (42.1)	
Cmax(ng/mL)	97.5 (51.3)	84.8 (57.1)	
Tmax (hr)	5.59	7.09	
Kel(1/hr)	0.079	0.080	
T1/2(hr)	9.48	9.31	
LnAUC(0-t)			86.4-106.7%
LnAUCinf			85.1-104.2%
LnCmax			99.5-141.0%

1. For Verapamil, the least squares means for AUC(0-t), AUCinf and Cmax values were 6.0%, 6.9% and 14.7% lower and higher, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for the AUC(0-t) and AUCinf are within the acceptable range of 80-125% for log-transformed data. The 90% confidence intervals for the Cmax is not within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

2. The Verapamil plasma levels peaked at 5 and 6 hours for the test and the reference products, respectively, following their administration under fasting conditions.

3. The firm indicated that the data for subject #7 was highly anomalous relative to the data from the other subject; i.e., the concentrations of verapamil observed following the reference dosage form (Knoll) were very low (Cmax = 8.70 ng/mL), the lowest of the entire population, relative to Duramed (Cmax = 51.88

ng/mL). The firm excluded subject #7 from the statistical analysis of the study. The resulting 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax after excluded the subject were as following:

Verapamil =

LnAUC(0-t)	84.7-103.3%
LnAUCinf	85.1-104.1%
LnCmax	86.1-131.4%

Norverapamil

LnAUC(0-t)	91.7-104.4%
LnAUCinf	91.2-103.6%
LnCmax	97.3-125.3%

Excluding subject #7 from the statistical analysis of the study did not change the outcome of the study conclusion with regard to the 90% confidence interval for LnCmax.

Table IV

Mean Plasma Norverapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 180 Verapamil HCl ER (1x180 mg Tablet) under Fasting Conditions
(N=35)

Time (hr)	Test Formulation Duramed Lot#960701S ng/mL (CV%)	Reference Formulation (Isoptin®) Lot#21290026 ng/mL (CV%)
0	0.00	0.00
1.0	2.024 (170.0)	2.471 (145.8)
2.0	14.795 (83.9)	14.775 (82.5)
3.0	38.736 (66.0)	29.325 (62.5)

4.0	55.006 (56.8)	41.992 (52.9)
5.0	73.788 (52.1)	57.143 (53.3)
6.0	79.599 (43.7)	63.921 (56.1)
7.0	75.752 (44.0)	66.815 (49.3)
8.0	67.461 (40.4)	65.361 (49.3)
9.0	61.695 (37.8)	60.753 (44.6)
10	55.923 (35.8)	59.061 (38.4)
11	49.560 (33.0)	52.049 (36.0)
12	46.462 (32.4)	49.738 (34.3)
13	41.683 (30.6)	46.057 (34.6)
14	38.180 (31.9)	41.453 (31.2)
16	30.763 (31.5)	33.683 (31.1)
24	20.372 (39.3)	23.589 (36.8)
36	7.794 (43.3)	9.272 (48.8)
48	3.516 (57.3)	4.001 (64.1)
72	0.123 (412.2)	0.132 (414.3)

AUC(0-t) (ng.hr/mL)	1191.6 (28.7)	1216.8 (28.9)	
AUCInf (ng.hr/mL)	1253.4 (28.4)	1291.9 (28.0)	
Cmax (ng/mL)	86.3 (38.9)	77.3 (41.8)	
Tmax (hr)	7.23	8.75	
Kel (1/hr)	0.071	0.071	
T1/2 (hr)	10.12	10.19	
LnAUC(0-t)			92.0-104.4%
LnAUCinf			91.2-103.6%
LnCmax			98.7-126.3%

1. For norverapamil, the least squares means for AUC(0-t), AUCinf and Cmax values were 2.1%, 2.9% and 11.3% lower and higher, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for the AUC(0-t) and AUCinf are within the acceptable range of 80-125% for log-transformed data. The 90% confidence intervals for the Cmax is not within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

2. The norverapamil plasma levels peaked at 6 and 7 hours for the test and the reference products, respectively, following their administration under fasting conditions.

VII. Study #941081 For Single-Dose, Two-Way Crossover On Verapamil HCl Extended Release Tablets, 240 mg, Under Fasting Conditions:

Objective: The objective of the study was to compare the bioavailability of verapamil-ER tablets manufactured by Duramed Pharmaceuticals, Inc., with that of Knoll product (Isoptin^R SR), following an oral administration of a single 240 mg dose (1x240 mg tablet) of each product under fasting conditions.

Study site:

Sponsor: Duramed Pharmaceuticals, Inc.

Study design: Single-dose, randomized, 2-way crossover, open-label, under fasting conditions.

Dosing date: April 20 and May 4, 1995.

Subjects: Thirty-six (36) healthy adult male subjects enrolled and 34 completed the study.

Selection and exclusion criteria were the same as study#950257 above.

Dose and

Treatments: Treatment A: 1x240 mg verapamil HCl ER tablet (Duramed), lot #950301, batch size Tablets, potency 100.1%, content uniformity 101.0% (CV=1.1%), administered

following an overnight fast.

Treatment B: 1x240 mg Isoptin®SR tablet (Knoll), lot #21300154, Exp. 1/96, potency 102.6% content uniformity 101.0% (CV=1.2%), administered following an overnight fast.

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, 16, 24, 36 and 48 hours after dosing. Plasma samples were immediately frozen.

Assay Methodology: Same as study#950257 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 7.0% and 4.3% to 6.2%, for verapamil and norverapamil, respectively. The accuracy were 97.5% and 98.8% for verapamil and norverapamil, respectively.

VIII. In Vivo Results:

Thirty-six (36) subjects enrolled and thirty-four (34) successfully completed both phases of the clinical portion of the study. Subjects #20 and 21 withdrew from the study 18 hours prior to period II dosing for personal reasons. Twenty adverse events [headache (10), nausea (1), tightness in chest (1), high PR interval (6), feels tired (1) and Dizziness (1)] were reported in the study to be probably or possibly drug related.

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

Table V
Mean Plasma Verapamil Concentrations and Pharmacokinetic
Parameters Following an Oral Dose of 240 Verapamil HCl
ER (1x240 mg Tablet) under Fasting Conditions
(N=34)

Time (hr)	Test Formulation Duramed Lot#950301 ng/mL (CV%)	Reference Formulation (Isoptin®) Lot#21300154 ng/mL (CV%)
0	0.00	0.00
1.0	9.180 (108.9)	6.124 (73.5)
2.0	32.378 (94.9)	31.148 (68.1)
3.0	61.164 (84.2)	60.764 (64.4)
4.0	95.305 (84.6)	84.912 (62.6)
5.0	108.811 (72.2)	100.445 (57.0)
6.0	107.502 (68.9)	94.299 (55.7)
7.0	86.581 (54.3)	79.554 (59.5)
8.0	79.146 (61.8)	72.083 (50.0)
9.0	73.213 (59.2)	63.903 (49.0)
10	62.694 (54.1)	56.247 (42.1)
11	55.152 (53.3)	50.433 (42.2)
12	47.672 (54.4)	43.687 (41.1)
16	28.205 (50.9)	25.270 (42.8)
24	18.284 (59.3)	15.235 (45.4)
36	7.018 (72.3)	5.891 (60.7)

	48	3.163 (88.0)	2.606 (85.1)
AUC(0-t) (ng.hr/mL)	1337.5 (53.2)	1192.7 (43.4)	
AUCinf (ng.hr/mL)	1400.5 (52.0)	1242.2 (42.7)	
Cmax (ng/mL)	126.8 (66.9)	111.3 (50.2)	
Tmax (hr)	6.20	5.74	
Kel (1/hr)	0.081	0.083	
T1/2 (hr)	9.30	8.800	
LnAUC(0-t)			93.6-118.4%
LnAUCinf			95.3-119.3%
LnCmax			89.3-123.13%

1. For Verapamil, the least squares means for AUC(0-t), AUCinf and Cmax values were 12.1%, 11.3% and 13.9% higher, respectively, for the test product than for the reference product. The differences were 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 same as those submitted by the firm.

2. The Verapamil plasma levels peaked at 5 hours for both the test and the reference products, following their administration under fasting conditions.

Table VI

Mean Plasma Norverapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Verapamil HCl ER (1x240 mg Tablet) under Fasting Conditions
(N=34)

Time (hr)	Test Formulation Duramed Lot#950301 ng/mL (CV%)	Reference Formulation (Isoptin®) Lot#21300154 ng/mL (CV%)
0	0.00	0.00
1.0	4.844 (62.9)	4.031 (71.0)

If you have any questions please call:

Anna Marie H. Weikel
Project Manager
(301) 594-0315

Sincerely yours,

Jerry Phillips 3/31/97
Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, Ohio 45213
(513) 731-9900

The Art of Leadership...
The Science of Change

February 10, 1997

Refuse to File
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Qua marie H. Weikel
3/6/97

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA for Verapamil Hydrochloride Extended Release Tablets, USP, 120, 180 and 240 mg

Dear Mr. Sporn:

Duramed Pharmaceuticals, Inc. (Duramed) submits today an original abbreviated new drug application (ANDA) seeking approval to market Verapamil Hydrochloride Extended Release Tablets, USP, 120, 180 and 240 mg, that are bioequivalent to the reference drug, Isoptin® SR Tablets, manufactured by Knoll Pharmaceutical Company pursuant to NDA # 19-152.

In accordance with the study protocols (refer to documents included in Section VI), Duramed conducted one *in vivo* bioequivalence fasted study using 120 mg tablets, one *in vivo* bioequivalence fasted study using 180 mg tablets, and three *in vivo* bioequivalence studies (fed, fasted, and steady-state) using 240 mg tablets.

Verapamil Hydrochloride Extended Release Tablets, USP, 120, 180 and 240 mg are stable and a two year expiration dating is requested for all package sizes. The two year expiration dating is supported by accelerated stability testing.

This ANDA consists of thirty-two (32) volumes. The archival copy (blue folders) of this application contains all the information required in the ANDA. The technical review copy (red folders) containing all the information in the archival copy with the exception of the Bioequivalence section. The Bioequivalence review copy (orange folders) contains the bioequivalence data as well as computer disks, in 3.5" format, containing ASCII files of the measured concentrations of the drug substance and the kinetic parameters for the bioequivalence study.

For detailed information on the organization of this application, please refer to the following "EXECUTIVE SUMMARY - Organization of the ANDA".

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Food and Drug Administration, North Brunswick Residential Post, North Brunswick, New Jersey.

RECEIVED

FEB 10 1997

GENERIC DRUGS

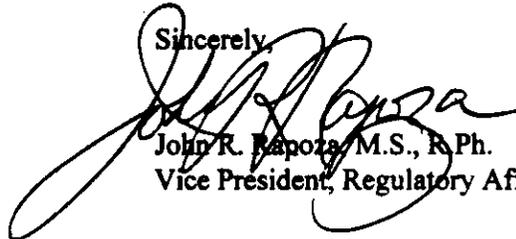
Page 2

To: Mr. Douglas L. Sporn

Subject: ANDA for Verapamil Hydrochloride Extended-Release Tablets, USP, 120, 180 and 240 mg

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please feel free to contact Mr. James Mason at (513) 731-9900, extension 7322, or me at (513) 731-9900, extension 7274 (513-731-6482 FAX).

Sincerely,

A handwritten signature in black ink, appearing to read "John R. Rapoza". The signature is fluid and cursive, with a large loop at the end.

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

2.0	17.793 (68.9)	19.092 (52.9)
3.0	34.325 (62.2)	36.262 (48.6)
4.0	54.551 (65.8)	53.871 (49.1)
5.0	64.208 (59.2)	66.006 (46.5)
6.0	71.452 (52.3)	69.616 (42.4)
7.0	66.475 (43.2)	65.089 (47.3)
8.0	66.229 (44.3)	64.119 (39.1)
9.0	66.511 (43.0)	62.179 (38.6)
10	61.155 (40.4)	57.809 (34.8)
11	57.437 (39.9)	54.919 (35.9)
12	53.183 (40.1)	52.094 (37.8)
16	37.851 (40.7)	36.589 (33.4)
24	27.414 (38.9)	24.940 (36.0)
36	12.345 (55.4)	10.743 (45.9)
48	6.290 (71.0)	5.683 (56.7)

AUC(0-t) (ng.hr/mL)	1380.7 (36.3)	1313.4 (32.7)	
AUCInf (ng.hr/mL)	1510.7 (36.7)	1420.8 (32.4)	
Cmax (ng/mL)	80.9 (46.0)	76.9 (38.4)	
Tmax (hr)	7.00	7.03	
Kel (1/hr)	0.063	0.064	
T1/2 (hr)	12.05	11.46	
LnAUC(0-t)			93.6-113.2%
LnAUCinf			95.0-114.0%
LnCmax			90.4-115.9%

1. For Norverapamil, the least squares means for AUC(0-t), AUCinf and Cmax values were 5.2%, 6.5% and 5.3% higher, respectively,

for the test product than for the reference product. The differences were 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 same as those submitted by the firm.

2. The Norverapamil plasma levels peaked at 6 hours for both the test and the reference products, following their administration under fasting conditions.

IX. Study #950281 For Post-Prandial, Single-Dose Bioequivalence Study, Three-way Crossover on Verapamil HCl ER Tablets, 240 mg

Study site:

Sponsor: Duramed Pharmaceuticals, Inc.

Study design: Single-dose, randomized, three-way crossover, open-label, under fasting and nonfasting conditions.

Dosing date: June 21, July 5 and 19, 1995.

Subjects: Twenty-four (24) healthy adult male subjects enrolled in the study. Subject #24 was withdrawn from the study by the study physician prior to period I dosing as his pre-dose blood pressure measurement did not meet the criteria specified in the protocol. As indicated in the protocol, data from subjects who completed at least 2 periods of the study were analyzed. Therefore, statistical and pharmacokinetic analyses were performed on data from 20 subjects (subjects #1, 2, 4, 5, 7-16 and 18-23). Selection and exclusion criteria were the same as study#950257 above.

Dose and

Treatments: Treatment A: 1x240 mg verapamil HCl ER tablet (Duramed), lot #950301, batch size ablets, potency 100.1%, content uniformity 101.0% (CV=1.1%), administered following an overnight fast.

Treatment B: 1x240 mg verapamil HCl ER tablet (Duramed), lot #950301, batch size [redacted], potency 100.1%, content uniformity 101.0% (CV=1.1%), administered Within 30 minutes of a high fat breakfast preceded by an overnight fast.
Treatment C: 1x240 mg Isoptin®SR tablet (Knoll), lot #21300154, Exp. 1/96, potency 102.6% content uniformity 101.0% (CV=1.2%), administered within 30 minutes of a high fat breakfast preceded by 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 A ingested the tablet with 240 mL of water. Subjects on regimen B and C ingested the tablet with 240 mL of water within 30 minutes after 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 4 and 9 hours, respectively, post-dose. Liquids were ad libitum after lunch.

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, 16, 24, 36 and 48 hours after dosing. Plasma samples were immediately frozen.

Assay Methodology: Same as study#950257 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 3.4% to 14.2% and 3.9% to 12.5%, for verapamil and norverapamil, respectively. The accuracy were 101.8% and 101.2% for verapamil and norverapamil, respectively.

X. In Vivo Results:

Twenty-four (24) subjects enrolled and a total of 19 subjects successfully completed all 3 phases of the clinical portion of the study. Four subjects did not complete the crossover. Subject #3 was withdrawn from the study by the study physician 3.2 hours after period I dosing, due to medical events judged by the study physician to be definitely related to the study procedures (bruises on left and right arms after blood draw). Subjects #6 and 17 elected to withdraw from the study at 12.7 and 15 hours prior to period 2 dosing, respectively, due to personal reasons. Subject #21 was withdrawn from the study by the study physician 1.2 hours prior to period III dosing due to low hemoglobin and hematocrit test results. Thus, a total of 19 subjects completed all 3 periods of the crossover. As indicated in the protocol, data from subjects who completed at least 2 periods of the study were analyzed. Therefore, statistical and pharmacokinetic analyses were performed on data from 20 subjects.

Two adverse events (headache) were reported in the study to be probably or possibly drug related.

The plasma concentrations and pharmacokinetic parameters for verapamil and norverapamil are summarized in Tables VII and VIII.

Table VII
Mean Plasma Verapamil Concentrations and Pharmacokinetic
Parameters Following an Oral Dose of 240 mg Verapamil
HCl ER Tablet Under Fasting and Nonfasting Conditions
(N=20)

Time	Test	Reference	Test
		(Isoptin®)	
(hr)	Duramed	Knoll	Duramed
	Lot	Lot	Lot
	#950301	#21300154	#950301
	ng/mL	ng/mL	ng/mL
	(CV%)	(CV%)	(CV%)
	Fed	Fed	Fasting
0	0.00	0.00	0.00
1	3.092	1.885	9.417
	(118.3)	(139.6)	(101.9)

2	12.113 (76.3)	9.557 (85.9)	46.236 (89.0)
3	23.127 (59.1)	15.292 (72.2)	86.108 (71.1)
4	36.278 (52.9)	24.190 (72.8)	120.438 (69.8)
5	51.975 (46.7)	40.446 (53.8)	139.159 (50.2)
6	59.511 (68.9)	36.999 (48.5)	119.895 (37.9)
7	58.147 (72.9)	44.813 (74.1)	98.289 (32.5)
8	57.123 (82.4)	45.623 (95.9)	76.709 (38.0)
9	64.897 (85.7)	49.725 (101.7)	71.251 (40.8)
10	59.970 (74.6)	50.981 (83.9)	52.343 (42.0)
11	60.814 (63.9)	50.930 (77.2)	48.390 (41.7)
12	57.142 (60.6)	50.623 (80.1)	44.114 (52.5)
16	44.075 (53.7)	33.304 (62.0)	28.881 (55.8)
24	38.994 (49.7)	30.960 (50.6)	16.865 (60.1)
36	12.113 (57.2)	11.501 (59.3)	5.335 (74.7)

48	6.080 (70.6)	5.822 (76.0)	2.922 (84.7)
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				Test Fed/ Reference Fed
AUC(0-t)				
(ng.hr/mL)	1461.2 (44.4)	1175.0 (52.1)	1388.2 (45.2)	1.24
AUCinf				
(ng.hr/mL)	1717.1 (42.5)	1386.7 (50.0)	1445.1 (44.2)	1.24
Cmax (ng/mL)	86.6 (64.7)	71.6 (71.6)	156.0 (44.2)	1.21
Tmax (hr)	12.15	10.16	5.05	
T1/2(hr)	11.10	13.43	8.84	
Kel(hr ⁻¹)	0.067	0.057	0.081	

Verapamil

1. The verapamil plasma levels peaked at 9 and 10 hours for the test and reference products, respectively, under nonfasting conditions and at 5 hours for the test product under fasting conditions.

2. For Duramed's test product, the mean AUC(0-t), AUCinf and Cmax values were 24.4%, 23.8% and 20.9% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic means to the reference arithmetic means are not within the acceptable range of 0.8-1.2 for the above parameters. The ratios of the least-squares means of the log-transformed parameters are as following:

AUC(0-T)	125.4
AUCinf	123.3
Cmax	122.3

The ratios of least-squares means of the log-transformed parameters AUCinf and Cmax for verapamil meet the criteria of 80-125%, the ratio for AUC(0-t) parameter slightly exceeds these limits.

3. It should be noted that the firm as stated in the protocol included first-order carryover effects in their model for the above statistical analysis. There was no carryover as indicated by P values of 0.9, 0.77 and 0.82 for LnAUC(0-t), LnAUCinf and

LnCmax, respectively. After excluding first-order carryover effects (by the reviewer) from the statistical analysis of the study, the resulting ratios of least-squares means of the log-transformed parameters for verapamil are as following:

LnAUC	125.7
LnAUCinf	120.9
LnCmax	124.3

The ratio for AUC(0-t) parameter exceeds limits of 80-125%.

4. For the test product, the mean Cmax value after dosing with food was about 55.5% of the value reported in the fasting state. Also, after feeding the Tmax was delayed about 7 hours relative to the fasting Tmax.

Table VIII
Mean Plasma Norverapamil Concentrations and Pharmacokinetic
Parameters Following an Oral Dose of 240 mg Verapamil
HCl ER Tablet Under Fasting and Nonfasting Conditions
(N=20)

Time (hr)	Test	Reference (Isoptin®)	Test
	Duramed Lot #950301 ng/mL (CV%) Fed	Knoll Lot #21300154 ng/mL (CV%) Fed	Duramed Lot #950301 ng/mL (CV%) Fasting
0	0.00	0.00	0.00
1	1.144 (150.0)	0.549 (252.3)	5.739 (78.9)
2	6.938 (67.5)	5.793 (93.8)	27.955 (68.0)

3	15.732 (44.3)	11.557 (54.6)	53.522 (56.2)
4	26.890 (33.5)	19.899 (52.2)	78.237 (53.5)
5	42.256 (24.1)	33.959 (36.2)	100.443 (46.0)
6	49.635 (37.1)	36.868 (30.9)	99.156 (39.7)
7	54.150 (42.2)	44.133 (41.5)	98.109 (34.4)
8	55.273 (49.3)	44.968 (49.4)	88.903 (32.1)
9	64.476 (48.3)	51.015 (51.4)	87.037 (32.9)
10	61.789 (48.9)	54.005 (46.6)	71.833 (29.7)
11	65.863 (44.3)	57.781 (45.6)	66.942 (29.9)
12	64.416 (46.4)	59.300 (53.8)	64.523 (35.5)
16	57.686 (33.9)	49.633 (38.9)	47.186 (32.7)
24	51.813 (30.7)	45.378 (31.3)	30.094 (40.3)
36	22.466 (34.2)	20.840 (39.0)	11.752 (51.5)
48	12.051 (47.7)	11.029 (53.4)	5.645 (70.9)

				Test Fed/ Reference Fed
AUC(0-t)				
(ng.hr/mL)	1818.1 (26.0)	1578.1 (27.9)	1687.7 (33.9)	1.15
AUCinf				
(ng.hr/mL)	2110.1 (27.6)	1886.6 (31.6)	1790.1 (34.0)	1.12
Cmax (ng/mL)	78.6 (39.1)	68.8 (43.6)	110.8 (36.0)	1.14
Tmax (hr)	15.10	13.74	6.40	
T1/2 (hr)	12.10	14.50	10.19	
Kel (hr ⁻¹)	0.061	0.054	0.071	

Norverapamil

1. The norverapamil plasma levels peaked at 11 and 12 hours for the test and reference products, respectively, under nonfasting conditions and at 5 hours for the test product under fasting conditions.

2. For Duramed's test product, the mean AUC(0-t), AUCinf and Cmax values were 15.2%, 11.8% and 14.2% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic means to the reference arithmetic means are within the acceptable range of 0.8-1.2 for the above parameters. The ratios of the least-squares means of the log-transformed parameters are as following:

AUC(0-T)	112.5
AUCinf	117.0
Cmax	114.7

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

3. It should be noted that the firm as stated in the protocol included first-order carryover effects in their model for the above statistical analysis. There was no carryover as indicated by P values of 0.9, 0.85 and 0.66 for LnAUC(0-t), LnAUCinf and LnCmax, respectively. After excluding first-order carryover effects (by the reviewer) from the statistical analysis of the study, the resulting ratios of least-squares means of the log-transformed parameters for norverapamil are as following:

LnAUC	115.2
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tablet (Duramed), lot #950301, batch size
Tablets, potency 100.1%, content
uniformity 101.0% (CV=1.1%), administered
following an overnight fast.

Treatment B

Day 1-6: 1x240 mg Isoptin®SR tablet
(Knoll), lot #21300154, Exp. 1/96, potency
102.6% content uniformity 101.0%
(CV=1.2%), administered following an
overnight fast.

Blood samples:

Blood samples were collected before the
initial dose, before drug administration
on days 4, 5 and 6 of each period and at
the following times post-dose on day 6: 1,
2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,
14, 16 and 24 hours after dosing. Plasma
samples were immediately frozen.

PR intervals:

12-lead EKGs were recorded for each
subject approximately 1 hour before the
first and sixth doses and within 16
minutes before the scheduled blood draws
at 1, 3, 6, 9, 12 and 24 hours following
the 6th drug administration.

Safety monitoring:

A one-lead EKG (lead II) was performed for
each subject prior to the 2nd through the
5th dose and at approximately 1, 3 and 6
hours following the 1st through the 5th
dose. Sitting blood pressure and heart
rate were measured before each drug
administration and at approximately 3, 6
and 9 hours after dosing on day 1. On day
6, vital signs were measured before dosing
and within 8 minutes before the scheduled
blood draws at 3, 6, 9, 12 and 24 hours.

Food and fluid

intake:

Subjects were required to fast overnight
prior to and 4 hours after, each dose.
Water intake was not allowed from two
hours before and 4 hours after each dose,
except for the dosing water (240 mL), but
was allowed at all other times.

Assay Methodology:

Same as study#950257 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 6.4% to 9.8% and 6.1% to 9.7%, for verapamil and norverapamil, respectively. The accuracy was 98.0% and 99.9% for verapamil and norverapamil, respectively.

XII. In Vivo Results:

Forty (40) healthy adult male subjects enrolled, 10 subjects did not complete the crossover. Ten additional subjects enrolled in the study. Of these 10 additional subjects (#41 to 50), four did not complete the crossover. Thus, a total of 36 subjects completed the crossover. The clinical study was conducted in two groups. Subjects #1, 2, 15, 18, 21, 22, 38, 41, 46 and 49 were withdrawn from the study due to medical events (pneumonia, dizziness, pressure in the head, nausea, headache, first degree AV block, second degree AV block and abnormal EKG). Subjects #10 and 48 elected to withdraw for personal reasons. Subjects #31 and 40 were withdrawn because of positive ethanol test results. A total of two hundred sixty eight (268) adverse events were reported in the study and were categorized to be definitely, probably or possibly drug related. One hundred forty eight (148) adverse events were reported for the test product (of these events, first degree AV block [1], heart palpitations [6], heart pain [1] and headache [51]). One hundred eighteen (118) for the reference product (of these events, first degree AV block [1], heart palpitations [1], headache [34], dizziness [3] and pain in the chest [1]). Statistical and pharmacokinetic analysis were not performed for verapamil in subject #47 because no data was available (the study samples for the subject were extracted on four separate occasions. In all cases the analytical runs failed to meet the acceptance criteria, therefore, there was no reportable data for subject #47).

The plasma concentrations and pharmacokinetic parameters for verapamil and norverapamil are summarized in Tables IX and X.

Table IX
Mean Verapamil Plasma Concentrations and Pharmacokinetic
Parameters Following a Multiple Dosing (6x240 mg Tablets) of
Verapamil HCl ER Tablets
(N=35)

Time After First Dose (hr)	Test Formulation Duramed Lot#950301 ng/mL (CV%)	Reference Formulation (Isoptin®) Lot#21300154 ng/mL (CV%)
0	0.00	0.00
96	31.191 (66.1)	29.090 (63.8)
120	37.753 (66.1)	34.428 (55.2)
144	44.009 (65.1)	38.298 (52.1)
145	54.578 (59.9)	50.835 (57.3)
146	93.631 (56.4)	99.512 (61.6)
147	140.255 (48.1)	135.362 (52.9)
148	196.584 (52.6)	170.762 (49.9)
149	200.735 (58.5)	183.095 (58.3)
150	176.397 (60.6)	162.742 (65.6)
151	147.220 (61.0)	142.480 (69.4)
152	121.991 (64.2)	117.787 (62.5)
153	103.773 (57.7)	96.718 (59.2)
154	86.130 (57.4)	83.642 (57.9)
155	74.169 (57.8)	70.951 (59.1)

156	65.742 (56.9)	64.669 (57.7)
157	62.032 (55.6)	58.405 (64.8)
158	58.238 (62.0)	51.272 (60.6)
160	51.024 (62.6)	47.693 (58.7)
168	38.196 (61.2)	38.802 (61.6)

90% CI

AUC(0-24) (ng.hr/mL)	2032.6 (51.9)	1926.8 (49.4)	
Cmax (ng/mL)	223.9 (51.0)	213.0 (49.0)	
Cmin (ng/mL)	33.7 (65.4)	30.2 (61.4)	
Tmax (hr)	4.8	4.9	
LnAUC(0-24)			94.4-111.9%
LnCmax			90.2-113.0%

Verapamil

1. The plasma verapamil levels peaked at 149 hours for both the test and the reference products.

2. For verapamil, the least squares means for AUC(0-24) and Cmax values were 5.3% and 4.8% 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. It should be noted that the firm used a statistical model to assess the group effect. The Division of Biometrics recommended using the following model:

$$Y = \text{SEQ SUBJ}(\text{SEQ}) \text{ PER TRT}; \quad (\text{whereas period} = 4)$$

Analysis of variance was performed by the reviewer using the above model, the resulting 90% confidence intervals for LnAUC(0-24) and LnCmax were as following:

Verapamil

LnAUC(0-24)	94.5-112.4%
LnCmax	90.7-113.8%

All confidence intervals remained within the acceptable 80-125% range.

4. It should be also noted that a single oral 240 mg dose of verapamil HCl was administered q24h for a total of six doses. The firm reported AUC(0-T) calculations and Cmax concentrations for each subject for verapamil and norverapamil from 144 to 168 hours instead of 120 to 144 hours.

Table X
Mean Norverapamil Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (6x240 mg Tablets) of Verapamil HCl ER Tablets
(N=36)

Time After First Dose (hr)	Test Formulation Duramed Lot#950301 ng/mL (CV%)	Reference Formulation (Isoptin®) Lot#21300154 ng/mL (CV%)
0	0.00	0.00
96	45.918 (40.5)	45.671 (40.5)
120	54.771 (40.7)	53.308 (33.0)
144	60.866 (43.0)	58.973 (31.6)
145	65.402 (36.6)	61.630 (32.7)
146	80.115 (34.3)	84.568 (34.7)
147	103.814 (29.8)	103.700 (33.2)
148	129.415 (32.6)	123.542 (32.1)
149	151.335 (35.5)	148.099 (30.8)
150	156.688 (40.0)	141.516 (34.6)

151	142.293 (40.8)	137.115 (41.4)
152	130.619 (45.4)	120.517 (38.0)
153	116.933 (39.5)	111.173 (39.4)
154	108.923 (39.8)	103.233 (40.0)
155	101.352 (41.7)	92.886 (38.1)
156	93.899 (41.0)	87.424 (39.5)
157	87.111 (36.7)	81.996 (40.4)
158	87.808 (42.1)	79.434 (37.3)
160	77.341 (40.6)	73.970 (35.5)
168	55.120 (40.9)	55.865 (38.7)

			<u>90% CI</u>
AUC(0-24) (ng.hr/mL)	2234.95 (34.9)	2141.07 (31.3)	
Cmax (ng/mL)	166.08 (36.0)	160.43 (32.3)	
Cmin (ng/mL)	51.4 (43.3)	50.3 (38.5)	
Tmax (hr)	5.6	5.9	
LnAUC(0-24)			97.4-109.7%
LnCmax			94.9-109.6%

1. The plasma norverapamil levels peaked at 149 and 150 hours for the reference and the test products, respectively.

2. For norverapamil, the least squares means for AUC(0-24) and Cmax values were 4.4% and 3.5% 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%.

XIII. Formulations:

**Duramed Verapamil Hydrochloride ER Tablet Granulation
Formulation Comparison by Dosage Strength**

Quantity per Tablet (mg)

Ingredient 120 mg Tablet 180 mg Tablet 240 mg Tablet

Tablet Kernel Composition

Verapamil Hydrochloride,	120.0	180.0	240.0
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XIV. In Vitro Dissolution Testing:

Method: USP 23 apparatus II (paddle) at 50 rpm

Medium: 900 mL of Simulated Gastric Fluid T.S (no enzyme) for one hour, then Simulated Intestinal Fluid T.S. (no enzyme) for 2, 3.5, 5 and 8 hours.

Number of

Tablets: Not given

Test Product: Duramed's Verapamil HCl ER tablets
240 mg, 180 mg and 120 mg

Reference

Product: Knoll's Isoptin^R SR tablets
240 mg, 180 mg and 120 mg

Specifications: The firm proposed the following specifications:

The dissolution testing results are presented in table XII.

The firm submitted comparative dissolution testing on six half tablets (test and reference products) for the 240 mg and 180 mg strengths.

XV. Comments:

1. The firm's single-dose bioequivalence study #941081 under fasting conditions, conducted on its 240 mg verapamil HCl ER tablet is acceptable. The 90% confidence intervals for $\text{LnAUC}(0-t)$, LnAUCinf and LnCmax are within the acceptable range of 80-125% for verapamil and norverapamil.
2. The firm's multiple-dose bioequivalence study #950282 under fasting conditions, conducted on its 240 mg verapamil HCl ER tablet is incomplete. The firm stated that a single oral 240 mg dose of verapamil HCl was administered q24h for a total of six doses. Blood samples were collected before the initial dose, before drug administration on days 4, 5 and 6 of each period and at the following times post-dose on day 6: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16 and 24 hours after dosing. The firm reported $\text{AUC}(0-T)$ calculations and Cmax concentrations for each subject for verapamil and norverapamil from 144 to 168 hours instead of 120 to 144 hours.
3. The firm's single-dose bioequivalence study #950281 under fasting and nonfasting conditions, conducted on its 240 mg verapamil HCl ER tablet is unacceptable. The ratios of the test arithmetic means to the reference arithmetic means are not within the acceptable range of 0.8-1.2 for $\text{AUC}(0-t)$, AUCinf and Cmax for verapamil under nonfasting conditions. The ratio of least-squares means of the log-transformed $\text{AUC}(0-t)$ parameter exceeds the acceptable range of 80-125% for verapamil under nonfasting conditions.
4. The firm's single-dose bioequivalence study #950257 under fasting conditions, conducted on its 120 mg verapamil HCl ER tablet is acceptable. The 90% confidence intervals for $\text{LnAUC}(0-t)$, LnAUCinf and LnCmax are within the acceptable range of 80-125% for verapamil and norverapamil.
5. The firm's single-dose bioequivalence study #950277 under fasting conditions, conducted on its 180 mg verapamil HCl ER tablet is unacceptable. The 90% confidence intervals for the LnCmax exceed the acceptable range of 80-125% for verapamil and norverapamil.

6. It should be noted that the above three strengths are quantitatively and qualitatively similar to each other.

XVI. Deficiency Comments:

1. The firm is advised to submit the dissolution testing results for each dosage unit (i.e., for each of the 12 whole and half tablets), for each strength in addition to mean, coefficient of variation and range for the dissolution testing data.

2. For the single-dose bioequivalence study #950281 conducted on the firm's Verapamil HCl ER Tablet, 240 mg, under fasting and nonfasting conditions, the ratios of the test arithmetic means to the reference arithmetic means are not within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax for verapamil under nonfasting conditions. The ratio of least-squares means of the log-transformed AUC(0-t) parameter exceeds the acceptable range of 80-125% for verapamil under nonfasting conditions.

3. For the multiple-dose bioequivalence study #950282 under fasting conditions, conducted on the firm's verapamil HCl 240 mg ER tablet, a single oral 240 mg dose of verapamil HCl was administered q24h for a total of six doses. The firm reported AUC(0-T) calculations and Cmax concentrations for each subject for verapamil and norverapamil from 144 to 168 hours instead of 120 to 144 hours. The firm should explain this discrepancy. The firm is advised to submit the dosing and sampling dates for each subject in the study.

4. For the single-dose bioequivalence study #950277 conducted on the firm's Verapamil HCl ER Tablet, 180 mg, the 90% confidence intervals for the Cmax exceed the acceptable range of 80-125% for log-transformed data for verapamil and norverapamil.

XVII. Recommendations:

1. The single-dose bioequivalence study #941081, conducted by Duramed Pharmaceuticals, Inc., on its verapamil HCl 240 mg extended release (ER) tablet, lot #950301, comparing it to Isoptin^R SR 240 mg tablet manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence.

2. The single-dose post-prandial bioequivalence study #950281, conducted by Duramed Pharmaceuticals, Inc., on its verapamil HCl

240 mg ER tablet, lot #950301, comparing it to Isoptin^R SR 240 mg tablet manufactured by Knoll Pharmaceuticals, has been found unacceptable by the Division of Bioequivalence for the reasons given in deficiency comment #2.

3. The multiple-dose steady-state bioequivalence study #950282, conducted by Duramed Pharmaceuticals, Inc., on its verapamil HCl 240 mg ER tablet, lot #950301, comparing it to Isoptin^R SR 240 mg tablet manufactured by Knoll Pharmaceuticals, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comment #3.

4. The single-dose bioequivalence study #950257, conducted by Duramed Pharmaceuticals, Inc., on its verapamil HCl 120 mg extended release (ER) tablet, lot #960702S, comparing it to Isoptin^R SR 120 mg tablet manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence.

5. The single-dose bioequivalence study #950277, conducted by Duramed Pharmaceuticals, Inc., on its verapamil HCl 180 mg extended release (ER) tablet, lot #960701S, comparing it to Isoptin^R SR 180 mg tablet manufactured by Knoll Pharmaceuticals, has been found unacceptable by the Division of Bioequivalence for the reason given in deficiency comment #4.

6. The dissolution testing conducting by Duramed Pharmaceuticals, Inc., on its verapamil HCl 240 mg, 180 mg and 120 mg ER tablets, is incomplete for the reason given in deficiency comment 1.

The firm should be informed of the deficiency comments recommendations.

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

Date:

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Concur: _____

Date: 8/4/97

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Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence

Mmakary/7-9-97 wp 75072SD.297

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product			Reference Product		
	Mean %	Range	%CV	Mean %	Range	%CV
	Lot # Strength(mg) 240			Lot # Strength(mg) 240		
1	12.8		5.5	9.8		7.7
2	21.7		5.6	17.2		7.8
3.5	43.2		4.0	38.2		9.1
5	66.5		5.0	60.0		8.8
8	99.4		2.1	95.9		5.1
	Lot # Strength(mg) 180			Lot # Strength(mg) 180		
1	12.9		7.5	10.7		3.3
2	20.2		5.2	17.5		3.5
3.5	39.1		4.0	37.4		5.0
5	59.8		3.9	58.3		5.5
8	93.1		3.5	92.4		4.2
	Lot # Strength(mg) 120			Lot # Strength(mg) 120		
1	14.4		6.7	12.3		4.6
2	22.7		5.8	17.6		10.3
3.5	43.2		5.6	36.9		14.9
5	65.2		5.0	56.5		11.7
8	98.0		3.1	90.7		6.5

Figure 1
Project No. 941081
Mean Human Plasma Verapamil Concentrations
(Linear Plot)

240 mg Fasting Study

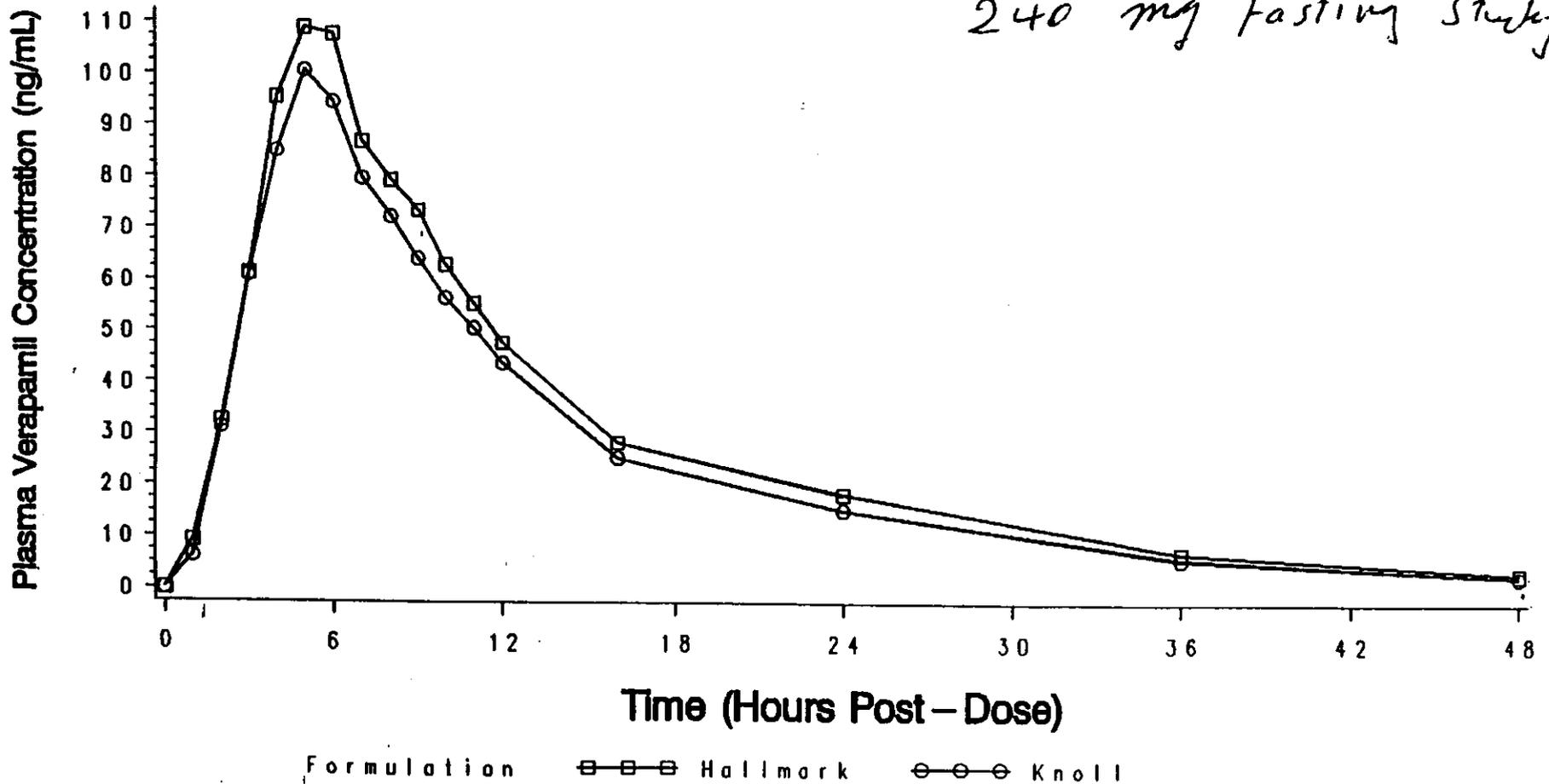


Figure 2
Project No. 941081
Mean Human Plasma Norverapamil Concentrations
(Linear Plot)

240 mg Fasting study

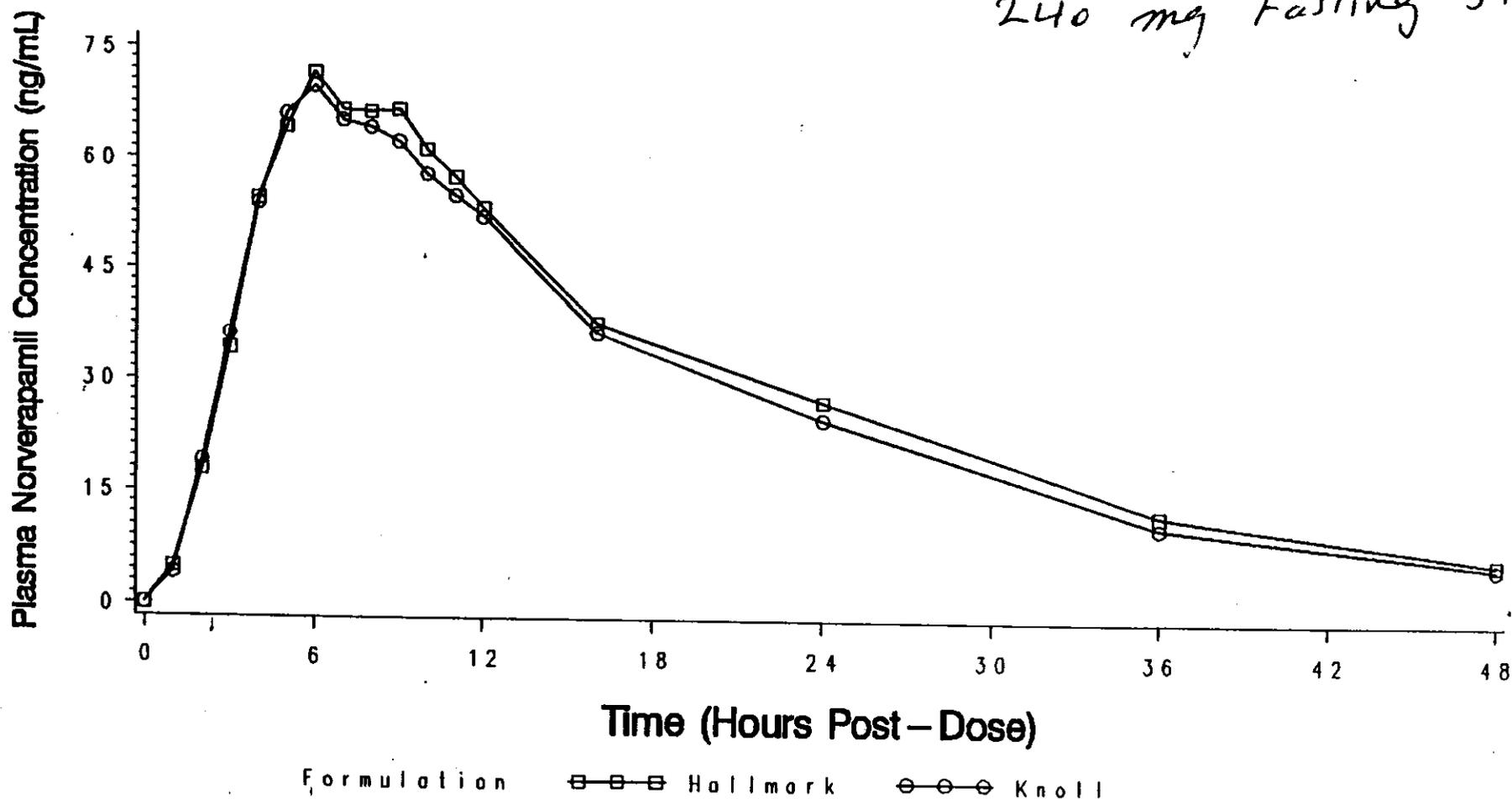
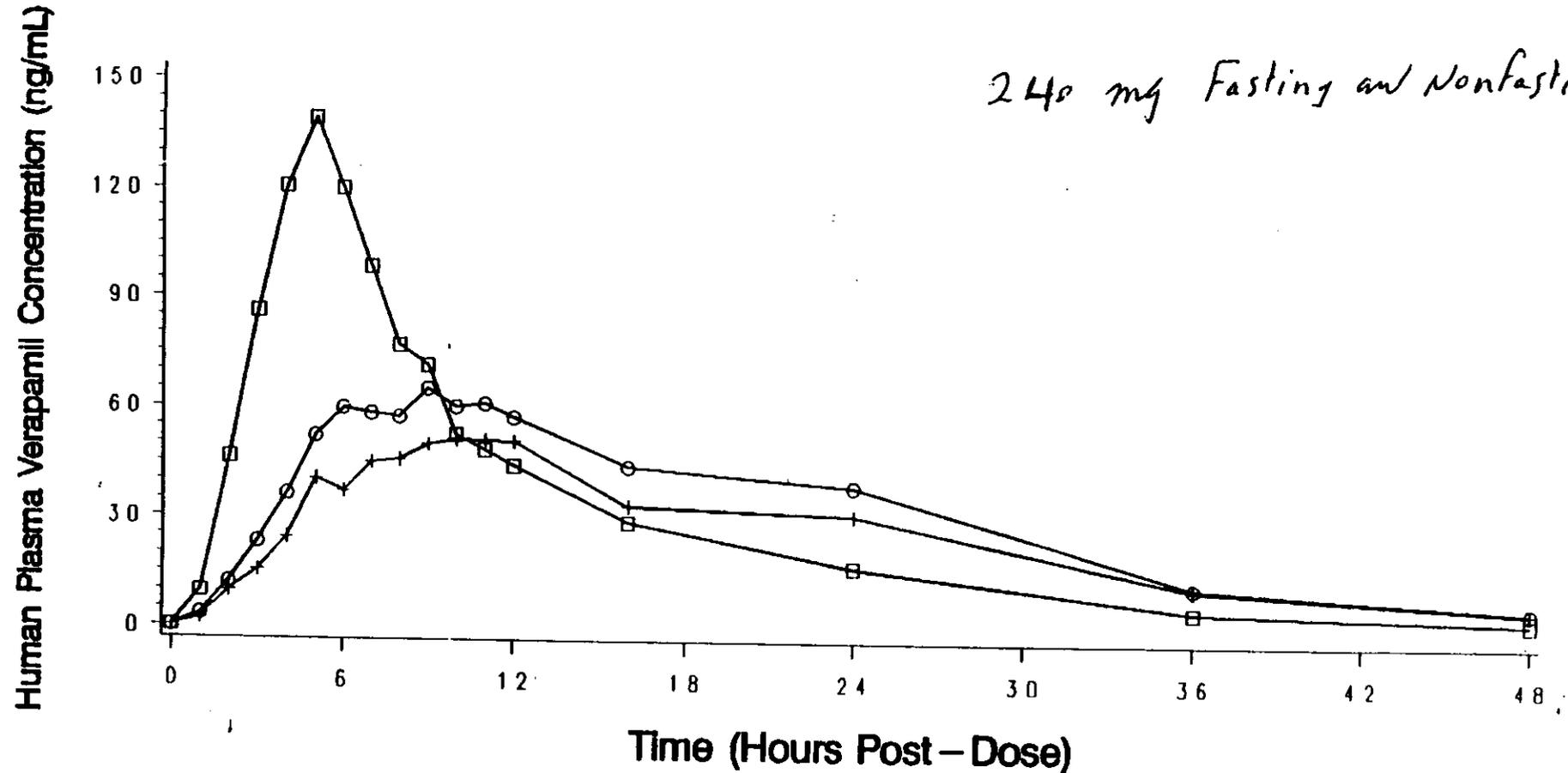


Figure ^{III}
 Project No. 950281
 Mean Human Plasma Verapamil Concentrations
 (Linear Plot)

240 mg Fasting and Nonfasting



Formulation □-□-□ Hallmark (fast), ○-○-○ Hallmark (fed)
 +--+ Knoll (fed)

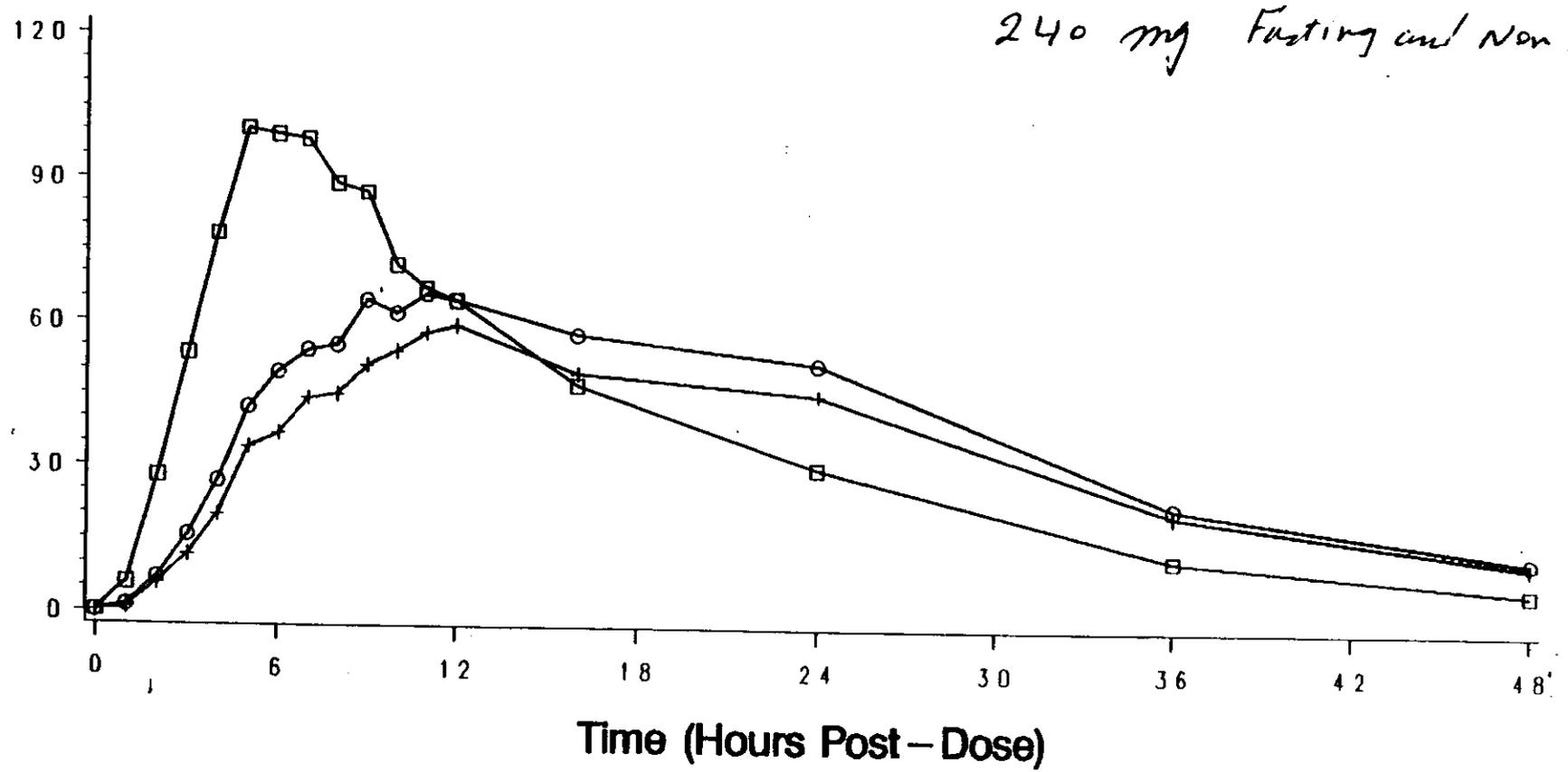
Figure

IV

Project No. 950281

Mean Human Plasma Norverapamil Concentrations
(Linear Plot)

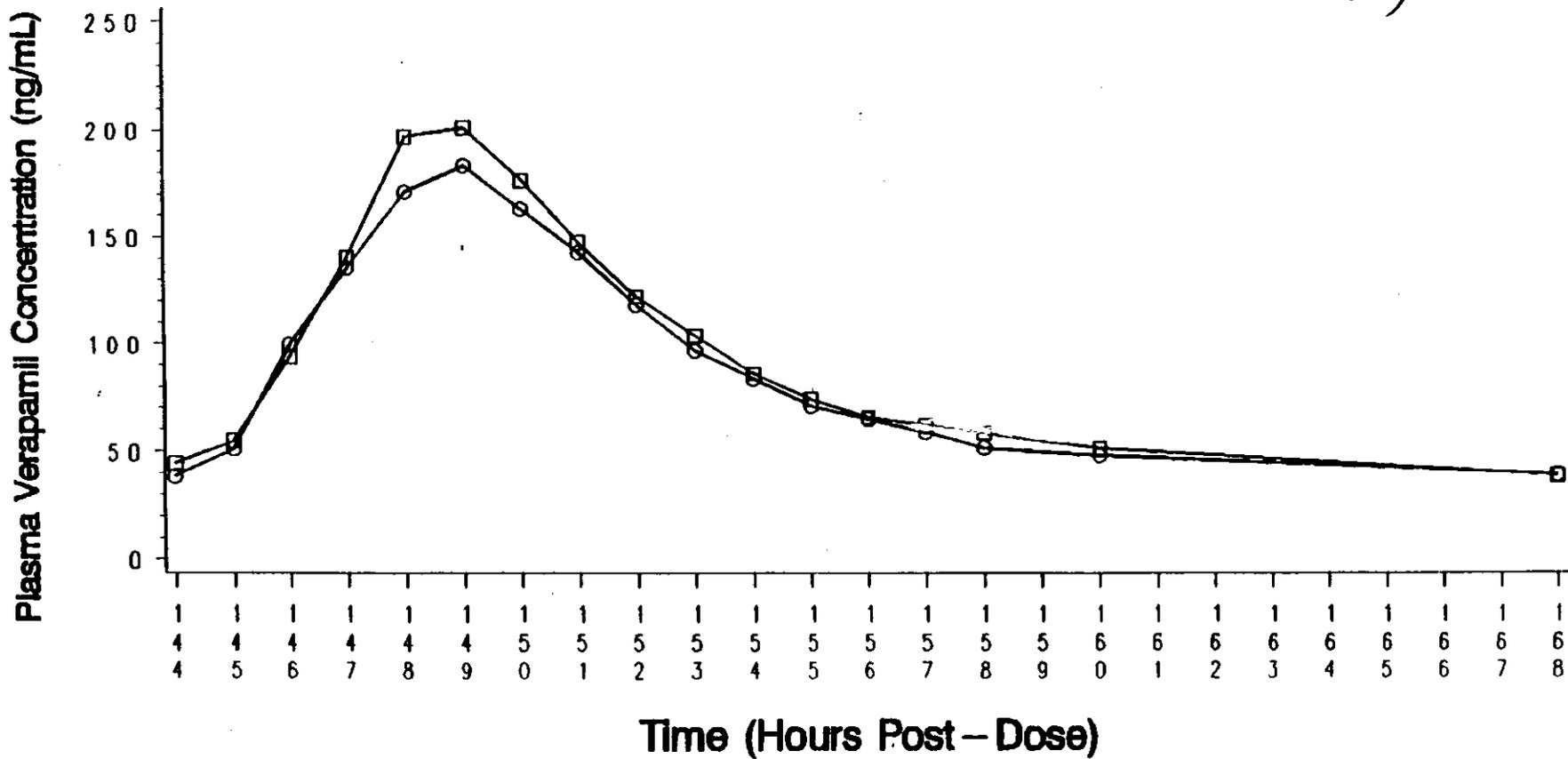
Human Plasma Norverapamil Concentration (ng/mL)



Formulation □-□-□ Hallmark (fast) ○-○-○ Hallmark (fed)
 +--+ Knoll (fed)

Figure . V
 Project No. 950282
 Mean Plasma Verapamil Concentrations
 (Linear Plot)

240 mg Steady-State



Formulation □-□-□ Hallmark ○-○-○ Knoll

Figure VI
 Project No. 950282
 Mean Plasma Norverapamil Concentrations
 (Linear Plot)

240 mg Steady-State

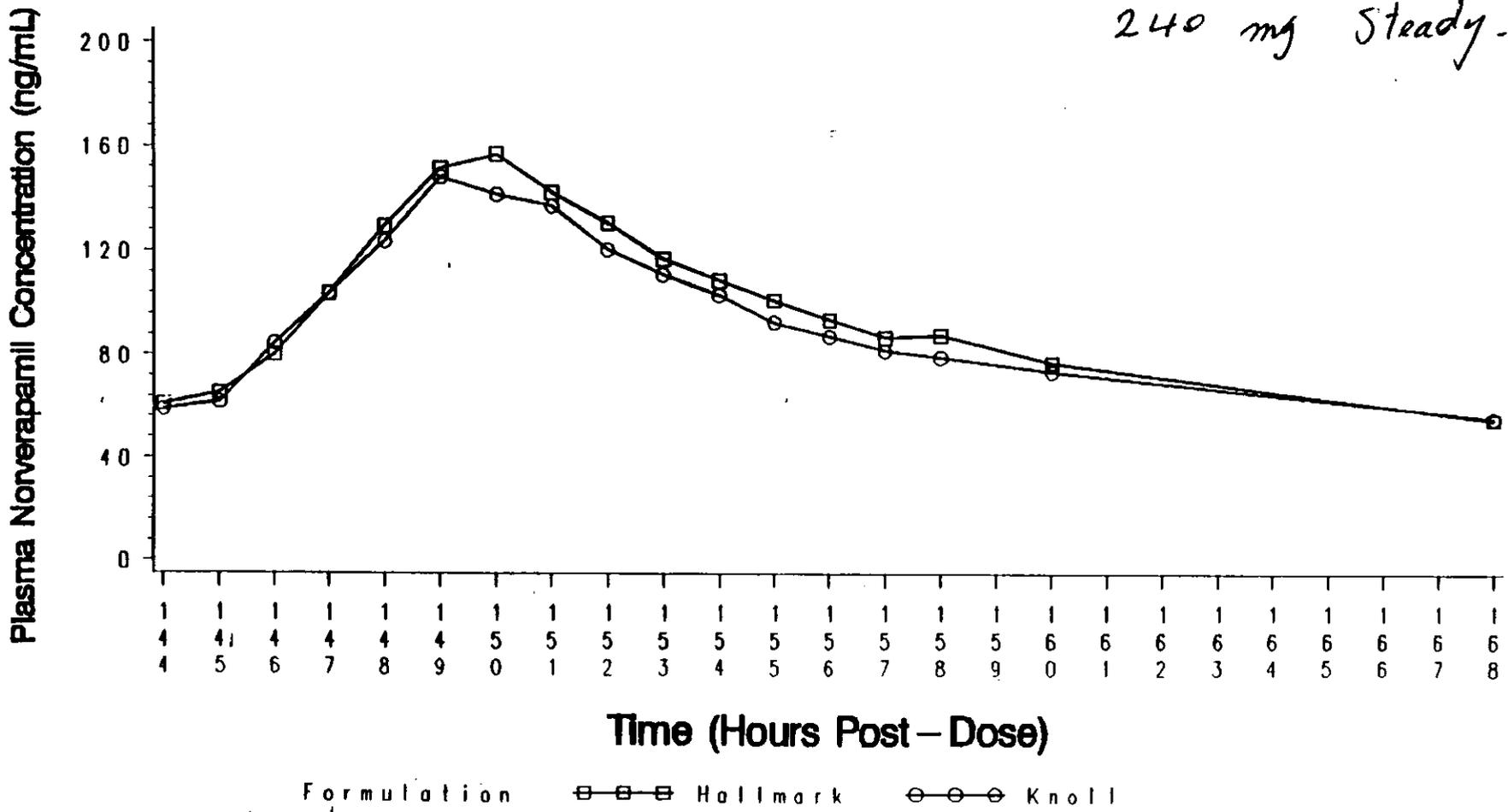


Figure VII
Project No. 950257
Mean Plasma Verapamil Concentrations
(Linear Plot)

120 mg

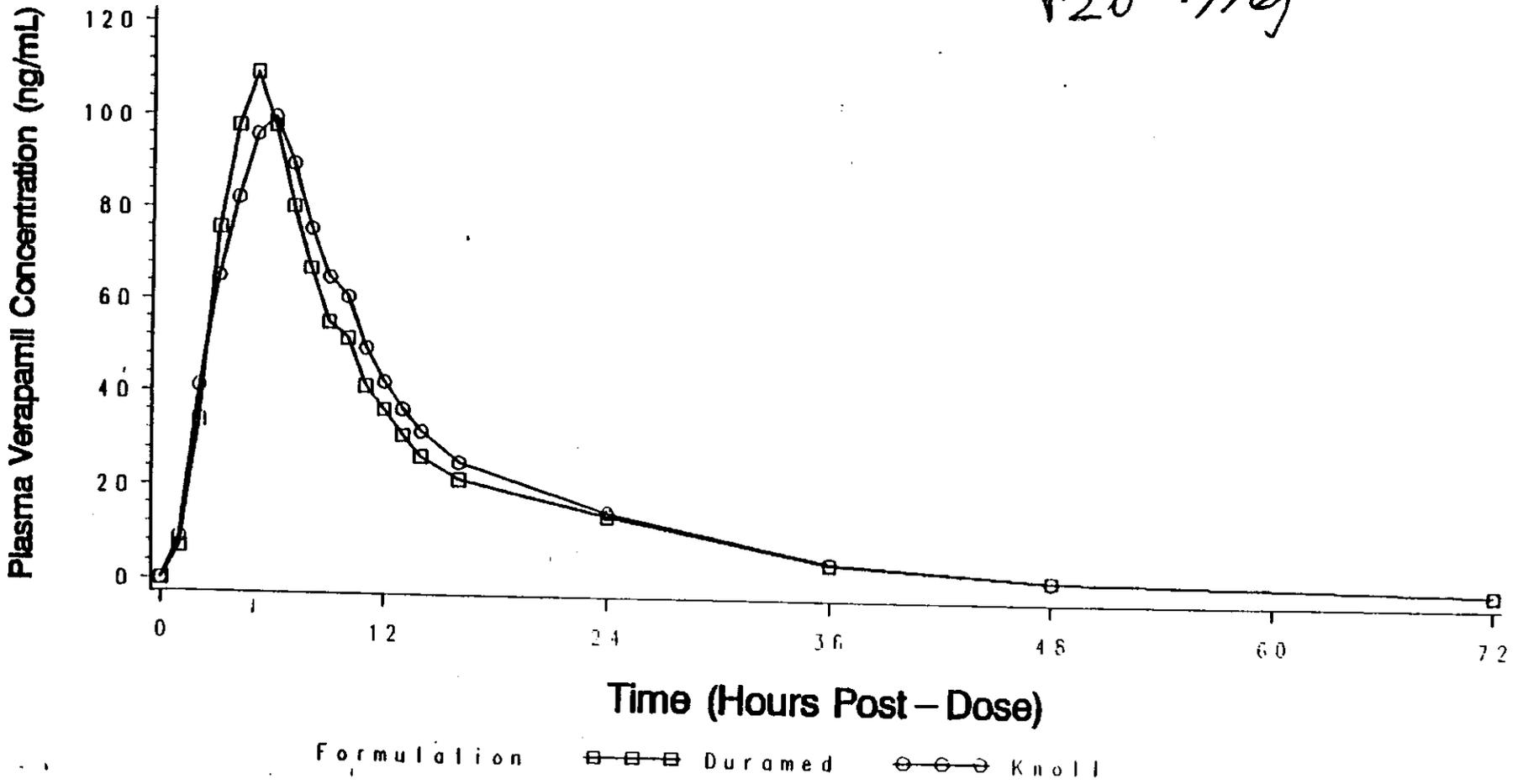


Figure VIII

Project No. 950257

Mean Plasma Norverapamil Concentrations
(Linear Plot)

120 mg

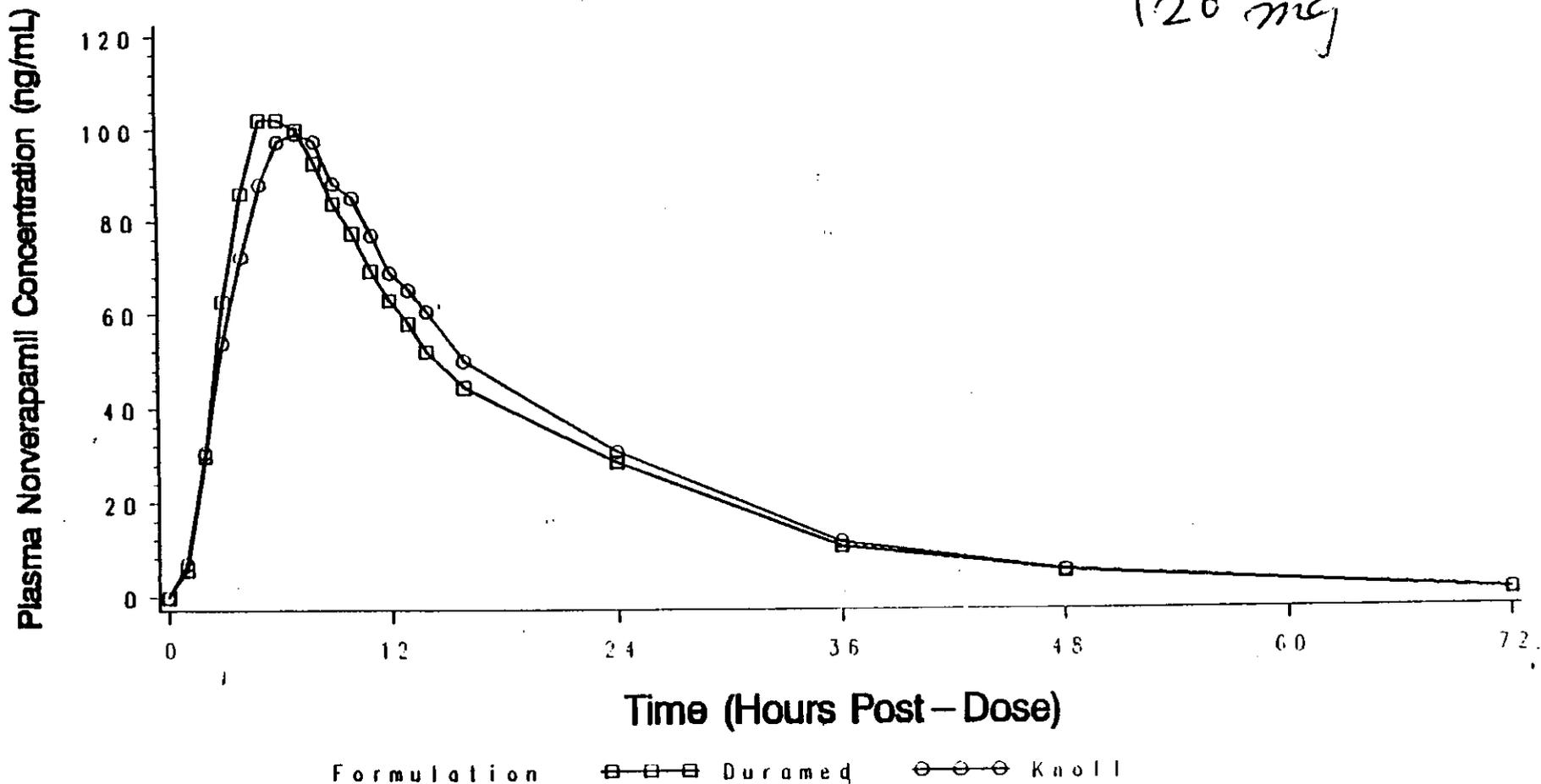


Figure IX
Project No. 950277
Mean Plasma Verapamil Concentrations
(Linear Plot)

180 mg

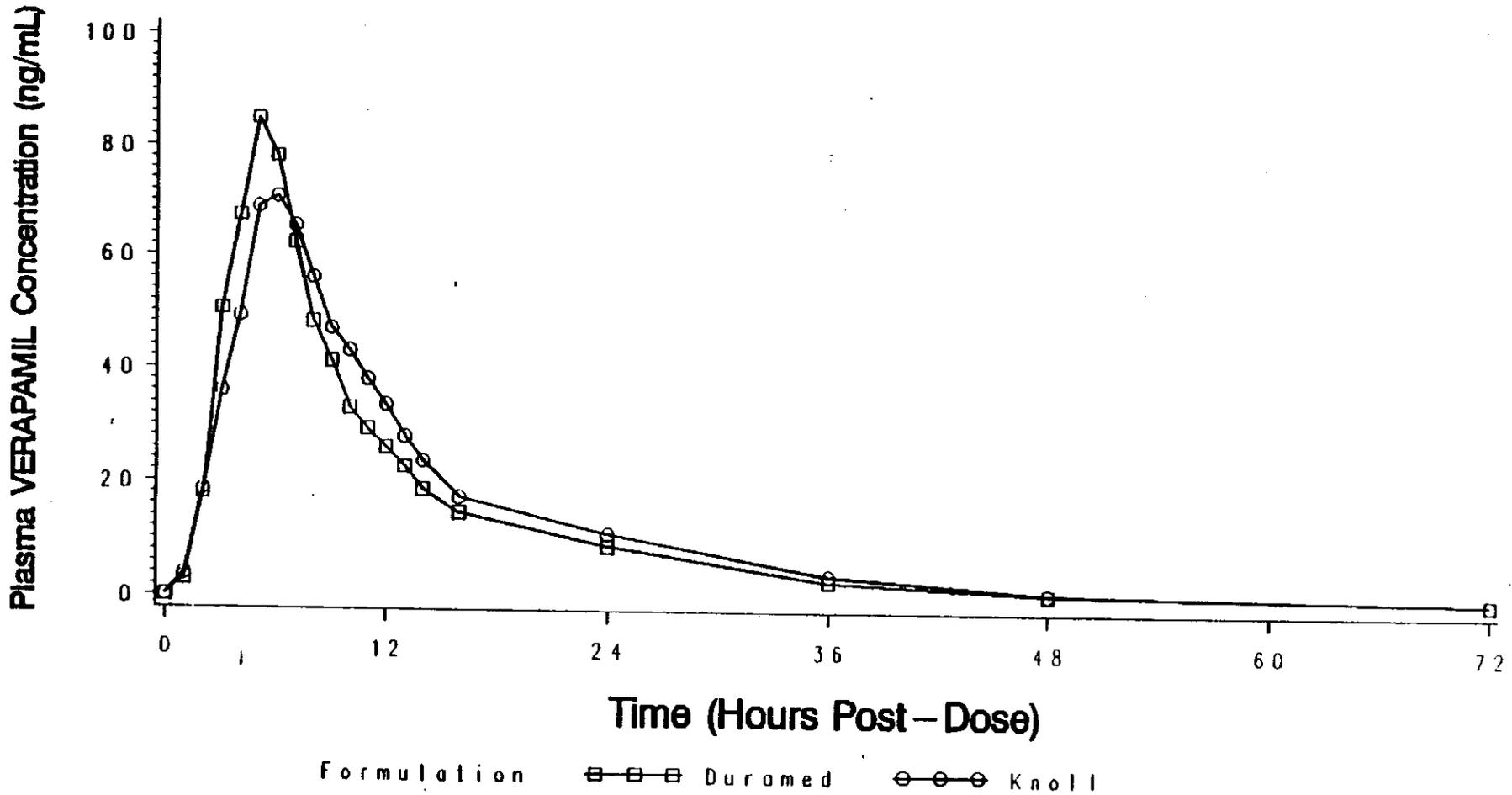


Figure *X*

Project No. 950277

Mean Plasma Norverapamil Concentrations
(Linear Plot)

180 mg

