CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20943

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

D. Arecler

AUG 12 1998

Biopharmaceutics/Pharmacokinetics Review

NDA: 20943

Sponsor: Elan Pharmaceutical Research, Gainesville, GA.

Drug: Verapamil PM (Verapamil Hydrochloride)

Formulation and Strengths: Extended Release Capsules 100, 200 and 300 mg

Drug class: Calcium Channel Blocker

Type of Submission: New dosage form

Date of Submission: December 23rd, 1997
May 12th, 1998

Reviewer: Nakissa Sadrieh, Ph.D.

Synopsis:

NDA 20-943 is for a delayed release formulation of verapamil to be given to hypertensive patients at night. This is to provide adequate blood pressure control in the morning hours, when blood pressure is usually at its highest levels.

The sponsor (Elan Pharmaceutical) uses the CODAS (Chronotherapeutic Oral Drug Absorption System) technology. The verapamil in the formulation is administered as a racemic mixture. The formulation has been designed to initiate release of the verapamil 4-5 hours after ingestion. The results from the studies submitted in this NDA show that when taken at bedtime, the verapamil is released with a lag time of 4 hours, reaching therapeutic blood levels in the early morning hours, when the blood pressure is at its highest.

The sponsor has carried out a single dose study in healthy volunteers, a food effect study, a steady state study, a dose proportionality study and an IVIVC study. All the

PK studies were conducted lot with 6H802 except in the dose proportionality study and the IVIVC study. In the dose proportionality study, lots 7C805, 806 and 807 were used. In the IVIVC studies, lots 6K802, 803, 803 and 804, which differed in their dissolution profiles, were used. Of these, lot 6K803 had a "medium" dissolution profile and was the closest to the lots which were used the clinical pharmacology studies.

In most studies, both R- and S- stereoisomers of verapamil were analyzed by

In a single dose study (study 0796006), Verapamil PM (200 mg) showed a 4 hour lag time prior to a rise in its blood levels. As compared to Isoptin, a marketed immediate release verapamil, the dose-adjusted bioavailability of Verpamil PM was 87%. Therapeutic levels were reached at 6-8 hours after dosing and peak blood levels were reached 10-12 hours after dosing. The Cmax for a 200 mg dose of verapamil was 56.43 ± 24.98 ng/ml, the AUC(0-inf) was 875.96 ± 419.57 ng.hr/ml, the Tmax was 11.42 ± 1.72 hours and the t ½ was 7.90 ± 2.46 hours. Additionally, compared to an immediate release verapamil (Isoptin) dosed 3 times a day at 80 mg per dose, lower peak to trough fluctuations were noted when one dose of Verapamil PM was given (200 mg).

With multiple dosing, a steady state was reached at 5 days (study 0896002). The value for the Cmax was 1.67 times higher after 5 daily doses, as compared with the single dose study. Compared with the reference drug Isoptin, the dose-adjusted bioavailability of Verapamil PM was 83% and lower peak to trough fluctuations were noted.

Over a range of 100-400 mg dose of Verapamil PM, dose-proportionality was not demonstrated. Norverapamil showed dose-proportionality over the dose range, however Verapamil did not. Verapamil showed some dose proportional increases in AUC and Cmax in the 200-400 mg range for the S enantiomer. For the R enantiomer, a dose proportional increase in the AUC was seen between the 300-400 mg dose range.

A study was conducted to determine if food interacted with the pharmacokinetics of verapamil (study 0896001). No food effect was seen, however, a 24% increase in the rate of absorption (Cmax) of R verapamil was noted in the fed state. Additionally, a 37% increase in the Cmax for R and S norverapamil was seen in the fed state. No significant change in the AUC for verapamil or norverapamil was seen in the fed state versus the fasted state.

Interestingly, in most studies, the plasma levels of the metabolite norverapamil (which has some pharmacologic activity) were higher than those of verapamil. Additionally, the plasma levels of R- verapamil tended to be about 5 times higher than those of S-verapamil (the active metabolite). This is in accordance with published reports.

The sponsor conducted a level A IVIVC study. A correlation was established which helped in the setting of the specifications (the specifications are listed below). However, the predictive value of the IVIVC for future waivers of bioequivalence studies remains to be determined.

Recommendation:

NDA 20-943 appears to meet the requirements of the Office of Clinical Pharmacology and Biopharmaceutics. The Division of Pharmaceutical Evaluation 1 recommends the following dissolution methodology and the following specifications:

In vitro dissolution: the medium to be used is distilled water adjusted to pH=3.0 with 0.1N HCl, using type I dissolution apparatus (basket) at a rotation speed of 75 rpm.

Dissolution specifications:

1 hour: %
4 hours: %
8 hours: %
11 hours: %
24 hours: %

The IVIVC is presently not deemed to be predictive, therefore it will not constitute sufficient grounds for obtaining a waiver for future bioequivalence studies.

Labeling comments should be forwarded to the sponsor.

Table of Contents:

Page Number

Appendices

Appendix 1: Study No. 0796006; Single dose study in healthy volunteers to evaluate bioavailability of Elan's Verapamil PM 200 mg formulation following night time dosing relative to Isoptin 80 mg tablets (Knoll Pharmaceuticals) dosed three times daily at eight hourly intervals.

Appendix 2: Study No. 0896001; A single dose study in healthy volunteers to assess the effect of food on the bioavailability of Elan's Verapamil PM 200 mg formulation.

Appendix 3: Study No. 0896002; A steady state study in healthy male volunteers to evaluate the Bioavailability of Elan's verapamil PM 200 mg formulation following night time dosing relative to Isoptin® 80 mg tablet (Knoll Pharmaceuticals) three times daily at eight hours interval.

Appendix 4: Study No. 0197005; A single dose study in healthy volunteers to evaluate the dose proportionality of the Elan verapamil formulation following night time administration of 100, 200, 300 and 400 mg doses.

Appendix 5: Study No. 1095006; A study in healthy volunteers to assess the effect of varying in-vitro dissolution rates on in-vivo performance of Elan's verapamil 240 mg formulation and Isoptin® 80 mg at single dose.

Background:

NDA 20-943 is for a delayed release formulation of verapamil to be given to hypertensive patients at night. This is to provide adequate blood pressure control in the morning hours, when blood pressure is usually at its highest levels.

Verapamil is a calcium channel antagonist that exerts its pharmacologic effects by influencing the influx of ionic calcium across the cell membrane of the arterial smooth muscle and contractile cells.

Verapamil is 90% absorbed when administered in an immediate release formulation. Due to first pass metabolism, only 20-35% of the parent compound reaches the systemic circulation.

Twelve metabolites have been identified in plasma, however, with the exception of norverapamil, all are present in trace amounts. The cardiovascular activity of norverapamil has been reported to be approximately 20% of verapamil.

Verapamil and norverapamil are both chiral molecules. It is reported that (S)- verapamil is 2.5-15 times more active than (R)- verpamil.

Blood pressure values follow a circadian rhythm with highest readings in the morning and lowest readings in the evenings. The sponsor has capitalized on this fact and has developed a new formulation of verapamil. Verapamil PM is designed to be dosed at night (200 mg dose). After an initial 4 hour lag time, plasma levels of the drug are expected to increase and reach therapeutic levels in the early morning, when blood pressure is at its highest, thus helping prevent major cardiac events. It is expected that this dosing regimen will provide adequate 24-hour control of blood pressure in patients.

The sponsor (Elan Pharmaceutical) uses the CODAS (Chronotherapeutic Oral Drug Absorption System) technology. The verapamil in the formulation is administered as a racemic mixture. The formulation has been designed to initiate release of the verapamil 4-5 hours after ingestion. The delay is introduced by the level of non-enteric release-controlling polymer applied to drug-loaded beads. The release-controlling polymer is a combination of water-soluble and insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water-soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water-insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug.

Several forms of verapamil are currently approved in the United States. These include the following:

Dosage form (Sponsor)	Indication	Recommended Dosage
Calan SR caplets (Searle) (sustained release caplets)	Management of Essential hypertension	up to 480 mg (240 mg bid) with food
Calan tablets (Searle) (immediate release tablets)	Treatment of Angina, Arrhythmias, Essential hypertension	up to 480 mg (240 mg bid)
Covera-HS tablets (Searle) (delayed release osmotic pump delivery system that relases drug 4-5 hours after ingestion)	Management of Hypertension and Angina	up to 480 mg at bedtime
Isoptin ampules 5 mg/2 ml	Supraventricular	For intravenous use: 5-10

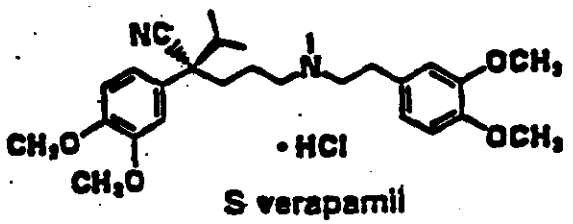
(Knoll Labs) (ampules for IV injection)	tachycardia, atrial flutter or atrial fibrillation	mg bolus over 2 minutes and repeat with 10 mg after 30 minutes.
Isoptin Oral tablets (Knoll Labs) (immediate release tablets)	Management of Essential hypertension	up to 480 mg (240 mg bid) with food
Isoptin SR tablets (Knoll Labs) (sustained release tablets)	Angina, Arrhythmias, Essential hypertension	up to 480 mg per day (regimen can be bid or tid)
Tarka tablets (Knoll Labs) (slow release formulation of verapamil combined with immediate release formulation of angiotensin converting enzyme enzyme inhibitor)	Hypertension (combination product: trandolapril/verapamil)	up to 4 mg trandolapril and 240 mg verapamil
Verelan capsules (Lederle Labs) (pellet-filled capsules containing sustained-release formulation of verapamil)	Management of Essential hypertension	up to 480 mg in the morning

The maximum recommended dose of verapamil is 480 mg per day.

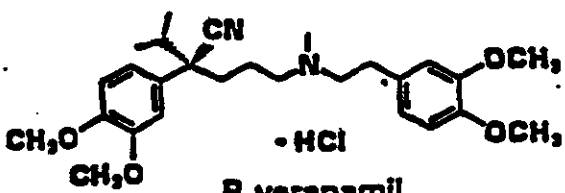
Summary of Results:

I. Physicochemical Properties:

Structure of verapamil



S verapamil



R verapamil

Verapamil HCl is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform and methanol.

II. Bioavailability and Disposition (Metabolism):

The sponsor has not carried out metabolism studies. However, a brief summary of previously published data on the disposition of verapamil will follow.

Verapamil is completely absorbed after oral administration. Due to extensive and stereoselective first pass, metabolism, on average only 20% of the drug reaches the systemic circulation. Patients with liver disease have a reported significant increase in bioavailability (52.3% vs. 22.0%). Peak plasma concentrations are achieved approximately 2 hours after oral administration. The volume of distribution of verapamil is 2.5-4.7 L/kg and is increased in liver disease, most likely due to an increase in total body water and tissue binding. Ninety percent of verapamil is protein bound to albumin and alpha-1-acid glycoprotein. Liver metabolism is extensive. One of the metabolites produced, noreverapamil, has weak pharmacologic activity and an elimination half-life of 4-10.5 hours. The elimination half-life of verapamil is 2-5 hours, which increases with liver disease and chronic oral dosing. Metabolites are excreted in the urine (70%) and feces (15%), with less than 5% of the parent compound excreted unchanged.

The bioavailability of the L- isomer of verapamil is significantly lower than that of the D- isomer. Stereoselective metabolism during first-pass elimination with oral dosing resulted in a decrease in the ratio of the L- (or S-) isomer to the D- (or R-) isomer delivered to the systemic circulation. The L- isomer is the potent isomer in producing a pharmacologic effect (negative ionotropic, negative chronotropic and negative dromotropic effect). Additionally, the L- isomer has an unbound fraction which is twice that of the D- isomer. This is reflected by a twofold difference in the volume of distribution for the 2 isomers (L- has larger volume of distribution than D- isomer). Since the oral clearance of the L- isomer is significantly greater than that of the D- isomer, the resulting peak plasma concentration of the D- isomer is five times greater than the L- isomer. However, the half-lives of the 2 isomers were similar.

Renal disease has no impact on the pharmacokinetics of verapamil.

III. Relative Bioavailability of verapamil PM:

In a single dose study (study 0796006), Verapamil PM (200 mg) showed a 4 hour lag time prior to a rise in its blood levels. Therapeutic levels were reached at 6-8 hours after dosing. The Cmax for a 200 mg dose of verapamil was 56.43 ± 24.98 ng/ml, the AUC(0-inf) was 875.96 ± 419.57 ng.hr/ml, the Tmax was 11.42 ± 1.72 hours and the

t ½ was 7.90 ± 2.46 hours. With nightime dosing , this delay in the rise blood levels is believed to provide therapeutic drug levels in the early morning hours, at a time when the blood pressure is expected to be at its highest. Peak blood levels were reached at approximately 10-12 hours after dosing. Compared to an immediate release verapamil (Isoptin) dosed 3 times a day at 80 mg per dose, lower peak to trough fluctuations were noted when one dose of Verapamil PM was given (200 mg). As compared to Isoptin, the dose-adjusted bioavailability of Verpamil PM was 87%.

The following is a table of the measured PK parameters for verapamil:

Parameter	Verapamil PM	Isoptin®
AUC (0-48) (ng/ml.h)	825.05 ± 417.26	1156.58 ± 483.58
AUC (0-inf) (ng/ml.h)	875.96 ± 419.57	1195.78 ± 496.73
Cmax (ng/ml)	56.43 ± 24.98	116.79 ± 38.45
F F(dose adjusted)	0.73 ± 0.19 0.87± 0.19	-
Tmax (h)	11.42 ± 1.72	15.53 ± 3.89
kel (h^{-1})	0.10 ± 0.03	0.13 ± 0.06
t ½ (h)	7.90 ± 2.46	6.07 ± 2.54

With multiple dosing, a steady state was reached at 5 days (study 0896002). The Cmax after 5 daily doses of verapamil PM at 200 mg per day was 94.51 ± 50.59 ng/ml. The value for the Cmax was 1.67 times higher after 5 daily doses, as compared with the single dose study, therefore, there was some drug accumulation. In fact, this is in accordance with studies in the literature which show that during long term treatment with verapamil, the bioavailability of the drug increases due to the saturation of first pass metabolism. The AUC (0-24h) was 1231 ± 684.97 and the Tmax was 10.83 ± 1.86 hours. The dose-adjusted bioavailability of Verapamil PM was 83% as compared to Isoptin. Again, lower peak to trough fluctuations were noted with Verapamil as compared with Isoptin. The bioavailabilty of Verapamil PM was comparable to the bioavailability of the drug after single oral dosing.

IV. Effect of Food, Posture and Time of Dosing:

Verapamil PM is to be dosed in the evening in order to provide adequate blood pressure control in the morning.

No food effect was seen (study 0896001). The extent of drug absorption was not affected by food intake. However, a 24% increase in the rate of absorption (Cmax) of R verapamil was noted in the fed state (68.29 ± 34.31 ng/ml in the fed state vs. 55.23 ± 26.38 ng/ml in the fasted state). Additionally, a 37% increase in the Cmax for R and S norverapamil was seen in the fed state (70.09 ± 33.27 ng/ml in the fed state vs. 51.59 ± 19.59 ng/ml in the fasted state). No significant change in the AUC for verapamil or norverapamil was seen in the fed state versus the fasted state. The AUC(0-48h) for verapamil was 923.13 ± 442.21 and 855.34 ± 452.23 ng.hr/ml in the fasted and fed state, respectively. The AUC(0-48h) for norverapamil was 1160.86 ± 422.50 and 1293.67 ± 476.82 ng.hr/ml in the fasted and fed state, respectively.

V. Dose Proportionality:

Over a range of 100-400 mg dose of Verapamil PM, dose-proportionality was not demonstrated. Norverapamil showed dose-proportionality over the dose range, however Verapamil did not. Verapamil showed some dose proportional increases in AUC and Cmax in the 200-400 mg range for the S enantiomer. For the R enantiomer, a dose proportional increase in the AUC was seen between the 300-400 mg dose range.

The following is a table of the ratios of the AUCs and Cmaxs dose-normalized to 100 mg. Please note that for (S)-verapamil, the data are dose-normalized to 200 mg, since the values for AUC and Cmax were below the detection limit at the 100 mg dose.

Parameter	100 mg	200 mg	300 mg	400 mg
(S)-verapamil				
AUC (inf)	below LOQ	-	1.35	2.2
Cmax	below LOQ	-	1.88	2.5
(R)-verapamil				
AUC(inf)	-	3	5.0	7.0
Cmax	-	2.72	5.15	6.4
(S)-norverapamil				
AUC (inf)	-	1.86	2.36	3.27
Cmax	-	1.99	3.38	4.18
(R)-norverapamil				
AUC (inf)	-	2.01	2.85	3.99
Cmax	-	2.36	3.84	4.71

VI. Formulation:

Verapamil PM lot compositions:

Component	100 mg capsule	200 mg capsule	300 mg capsule
Verapamil HCl	mg	mg	mg
Fumaric acid	mg	mg	mg
Talc	mg	mg	mg
Sugar Spheres	mg	mg	mg
Povidone	mg	mg	mg
Shellac	mg	mg	mg
Hard gelatin capsule	mg	mg	mg

VII. In Vitro/In Vivo Correlation (IVIVC):

The sponsor carried out a level A IVIVC. Initially, a deconvolution method was used in the determination of the IVIVC using Isoptin (80 mg) as the reference immediate release drug for the estimation of the PK parameters. It was observed that the IR AUC was lower for a majority of subjects than the ER AUC. The underestimation in the impulse response was reported to result in an underestimation in the PK parameters of the ER products outside of the allowable range for a predictable correlation. Therefore a convolution-based approach in which the IR results were not used for estimating the impulse response was used for the development of the IVIVC. The IVIVC developed using the convolution-based approach excluded the slowest batch tested (batch 802).

The sponsor concludes that the convolution-based IVIVC was predictable based on the predictions errors being within the limits of the FDA guidance. The reviewer did not agree with the method employed by the sponsor to establish the IVIVC. The average AUC profiles were determined for each lot and for all lots combined. In this analysis, convolution data provided by the sponsor for all 4 batches were used as well data from only 3 batches (where the "very slow" batch results were excluded). This analysis did not yield satisfactory prediction errors (Table 1, convolution analysis, 3-batches, lot 804). Therefore, the dissolution data for 2 additional lots, not used in the development of the IVIVC, were fitted to an Emax model and used to calculate the input function as absorption rate. Both input and elimination functions were convolved to obtain the predicted plasma profiles corresponding to the dissolution profiles. This resulted in predicted values for the AUC and Cmax which were quite different from those that

were observed in the PK studies. The prediction errors for the predicted versus observed AUC and Cmax ranged from 22% to 43%, regardless of whether the very slow (802) or the fast lot (804) was excluded from the analysis. Therefore, the analyses indicate that the external predictability of the model is inadequate no matter which lot is excluded from the calculations. Since the sponsor had not carried out an external predictability test using the model used in the convolution-based approach, the reviewer concludes that the IVIVC developed by the sponsor is not predictable.

In conclusion, the convolution-based approach gave better results due to the fact that the sponsor predicted the individual plasma profile for each subject using the average dissolution for each formulation and the individual disposition parameters for each subject. This procedure will minimize the variability and would thus result in more favorable prediction error values. Additionally, although the values of the prediction errors obtained in the convolution-based IVIVC do not indicate a need for an external predictability test, such a test would have been useful in determining the predictability of the model established by the sponsor. The reviewer used the dissolution data provided by the sponsor to determine prediction errors in the absence of lot 802 (very slow dissolution) and lot 804 (fast dissolution). However, these analyses did not yield acceptable prediction errors.

It should also be noted that in developing an IVIVC, it is generally customary to use the same drug in the IVIVC as that for which approval is being sought, and not another drug or formulation. In this particular case, since Verelan is very similar to verapamil PM, there will be no impact on the acceptability of the IVIVC.

Therefore, should the sponsor wish to use this IVIVC in justifying the waiver of future bioequivalence studies, the external predictability of the IVIVC should be undertaken to demonstrate the adequate predictive performance of the IVIVC model.

VIII. Dissolution:

Elan's Verapamil PM formulation was tested in vitro using 1000 ml distilled water adjusted to pH=3.0 with 0.1N HCl, using type I dissolution apparatus (basket) at a rotation speed of 75 rpm. It is reported that this is the officially approved dissolution method previously used for the development of Verelan SR and currently routinely used in its manufacture and control. The pH of the dissolution test is considered appropriate for the product, based on the pH solubility profile of verapamil HCl which has reduced solubility at higher pHs.

The dissolution specifications requested by the sponsor were as follows:

1 hour: %

4 hours: %
8 hours: %
11 hours: %
24 hours: %

The dissolution profiles from the following lots used in the clinical pharmacology studies were averaged to obtain an average dissolution profile. The average dissolution profile was convolved to obtain the predicted PK parameters (AUC, Tmax and Cmax). Additionally, the upper and lower limit dissolution profiles (from the specifications set forth by the sponsor) were also convolved to obtain the upper and lower limit predicted PK parameters. The upper and lower limit predicted PK parameters were compared to the average predicted PK parameters. The values obtained were as follows:

	Lower	Average	Upper
Cmax (ng/ml)	71.19	73.82	80.55
AUC (ng.hr/ml)	964.35	1097	1212
Tmax (h)	12.05	9.52	7.7

The predicted Cmax and AUC of the average dissolution profile was compared to the predicted Cmax and AUC values convolved form the upper and lower limit of the dissolution specifications. The percent difference is listed below:

	Upper limit	Lower limit
Cmax	9.0%	3.5%
AUC	10.48%	12.09%

The above-listed dissolution specifications are acceptable.

Comments to the Medical Division:

Comments to the Sponsor:

Labeling Comments (Pharmacokinetics and Metabolism):

The "Pharmacokinetics and Metabolism" section of the package insert is essentially identical to that of Covera-HS.

The following changes **(in bold)** are recommended.

The table in the "Pharmacokinetics and Metabolism" section of the package insert describes the pharmacokinetic characteristics of verapamil enantiomers after multiple dosing using the log10 transformed data. It is recommended that the non-transformed data be used in this table. The table should then be replaced with the following table:

The statement in the package insert which states:

should be replaced with

Under "Drug Interactions", the first paragraph should be replaced with the following paragraph:

/S/

Nakissa Sadrieh, Ph.D.

Date: 8/12/98

/S/

RD/FT Patrick Marroum, Ph.D. Date: 8/12/1998.

Biopharm day: August 6th, 1998 (Marroum, Malinowski, Mehta, Robbie, Selen, Hunt, Sadrieh)

CC List: NDA , HFD-110 (CSO); HFD-860 (Sadrieh, Marroum), HFD-340 (Wiswanathan).

Appendix 1

A single dose study in healthy volunteers to evaluate the bioavailability of Elan's Verapamil PM 200 mg formulation following night time dosing relative to Isoptin ® 80 mg tablets (Knoll Pharmaceuticals) dosed three time daily at eight hourly intervals.

Study No. 0796006 Volume 1.13-14 Pages 1-298

Study initiated January 14th, 1997
Study completed February 7th, 1997

Investigators:

Objectives:

Primary: To evaluate the bioavailability of Elan's Verapamil PM 200 mg formulation following night time dosing relative to Isoptin ® 80 mg tablet (Knoll Pharmaceuticals) three times daily at eight hourly intervals with both medications dosed at night.

Secondary: To monitor the volunteers for adverse events.

Medication:

Verapamil PM 200 mg capsule (Elan) Lot # 6H 802 (certificate of analysis provided for review) under fasting conditions (4 hours prior to dosing and 10 hours after dosing). It is assumed that the formulation used is identical to the "to be marketed formulation".

Isoptin ® 80 mg tablet (Knoll Pharmaceuticals) Lot # 20800056 under fasting conditions (4 hours prior to dosing on day one and remained fasting for two hours after the second dose).

Subjects were sitting or ambulatory for two hours after dosing and then supine for 8 hours following the evening dose of the medication.

Dose level:

An oral dose of 200 mg or 240 mg Verapamil in each treatment period.

Study population:

Twenty five subjects started the study but one subjects dropped out due to the flu prior to the commencement of period 2. Twenty-four (24) healthy volunteers aged between 18 and 40 years were therefore used. Five of the volunteers were non-smokers.

Design:

Open label two treatment, two period, two sequence balanced, randomized, crossover study with up to a seven day washout between treatments. The study protocol was approved by an independent ethical committee, an IRB, the Irish Medicines Board and the Department of Health. Twenty-four healthy subjects (19-39 years, body weight 65-105 kg) completed this study. All subjects were determined to be in good health through medical history, physical examination, ECG and laboratory tests (hematology, clinical chemistry, urinalysis, HIV, Hepatitis B surface antigen tests and a drug screen for drugs of abuse).

Subjects received an Elan 200 mg verapamil PM capsule at 10 pm or Isoptin ® 80 tablet, at 10 pm, 6 am and 2 pm according to a table of randomisation.

Venous blood specimens (7 ml) were obtained at the following time points:

> Test medication: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36 and 48 hours after dosing.
>
> Reference: pre-dose, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 8.25, 8.5, 8.75, 9, 9.5, 10, 11, 12, 14, 16, 16.25, 17, 17.5, 18, 19, 20, 22, 24, 30, 36 and 48 hours after dosing.

Plasma was isolated and frozen at -20 °C.

Assay procedures:

Data analysis:

The following calculations were performed on the plasma verapamil and norvarapamil concentrations of all 24 subjects:

AUC (0-48)	AUC(t1-t2)=(t1-t2)*(c2+c1)/2
AUC(infinity)	AUC(0-Clast)+(Clast/kel)
Cmax	observed maximal plasma concnetration
tmax	time at which Cmax is observed
kel	negative slope for the natural log of the detectable plasma concentration after Cmax versus time curve.
t ½	0.693/kel

Statistical analysis: Analysis of Variance (ANOVA) was performed on the pharmacokinetic parameters using General Linear Models procedures of SAS. 90% confidence intervals were calculated using least squares mean values for the treatments. *(Reviewer's comments: calculation of the 90% confidence interval in order to compare the 2 treatments was not necessary since treatments A and B differ in the dose given to the subjects. Verapamil PM was given at 200 mg per subject, whereas Isoptin® was given at 240 mg per subject)*

Results:

The following calculated pharmacokinetic parameters are reported:

Mean Verapamil pharmacokinetic parameters (Mean ± SD)

Parameter	Verapamil PM	Isoptin®
AUC (0-48) (ng/ml.h)	825.05 ± 417.26	1156.58 ± 483.58
AUC (0-inf) (ng/ml.h)	875.96 ± 419.57	1195.79 ± 496.73
Cmax (ng/ml)	56.43 ± 24.98	116.79 ± 38.45
F F(dose adjusted)	0.74 ± 0.19 0.87± 0.19	-
tmax (h)	11.42 ± 1.72	15.53 ± 3.89
kel (h^{-1})	0.10 ± 0.03	0.13 ± 0.06
t ½ (h)	7.90 ± 2.46	6.07 ± 2.54

Mean Norverapamil pharmacokinetic parameters (Mean ± SD)

Parameter	Norverapamil PM	Isoptin®
AUC (0-48) (ng/ml.h)	1507.35 ± 480.16	2226.03 ± 582.68
AUC (0-inf) (ng/ml.h)	1655.16 ± 540.90	2368.32 ± 624.46
Cmax (ng/ml)	81.92 ± 20.61	120.47 ± 27.99
F F(dose adjusted)	0.70 ± 0.13 0.84 ± 0.16	-
tmax (h)	12.58 ± 1.72	2.10 ± 0.97
kel (h^{-1})	0.07 ± 0.03	0.08 ± 0.02
t ½ (h)	10.30 ± 3.54	9.38 ± 2.27

Statistical analysis indicated that the pharmacokinetic parameters for Verapamil PM were significantly lower that those for Isoptin®, with the confidence intervals for these parameters being outside the bioequivalence limits. Additionally, plasma concentrations for norverapamil were generally higher than verapamil. Please refer to the included figures for illustration of these findings.

Conclusions:

The Elan formulation of Verapamil PM shows a plasma profile with the sponsor's claim regarding the 4 hour lag time prior to the rise in blood levels. Blood levels appear to peak at around 11 hours after dosing. However, when the drug is taken at night, the sponsor states that therapeutic levels are reached 6-8 hours after dosing, and consequently prior to waking.

In this study, 200 mg of Verapmil PM was compared to 240 mg (3 times 80 mg) Isoptin® (an immediate release formulation of verapamil) and was shown to have lower AUC and Cmax. This was to be expected considering the difference in the two doses. The sponsor also adds that the lower AUC and Cmax for Verapamil versus Isoptin® also provides for lower peak-to-trough fluctuations at steady state.

Reviewer's comments:

In the assay description section of the submission, it is not specified whether the R and S enantiomers were separated for both verapamil and norverapamil. It is also not indicated whether a chiral column was used in the separation.

Figure 1

Verapamil Plasma Concentrations Following PM Dosing

Protocol# 0796006 - Mean Data

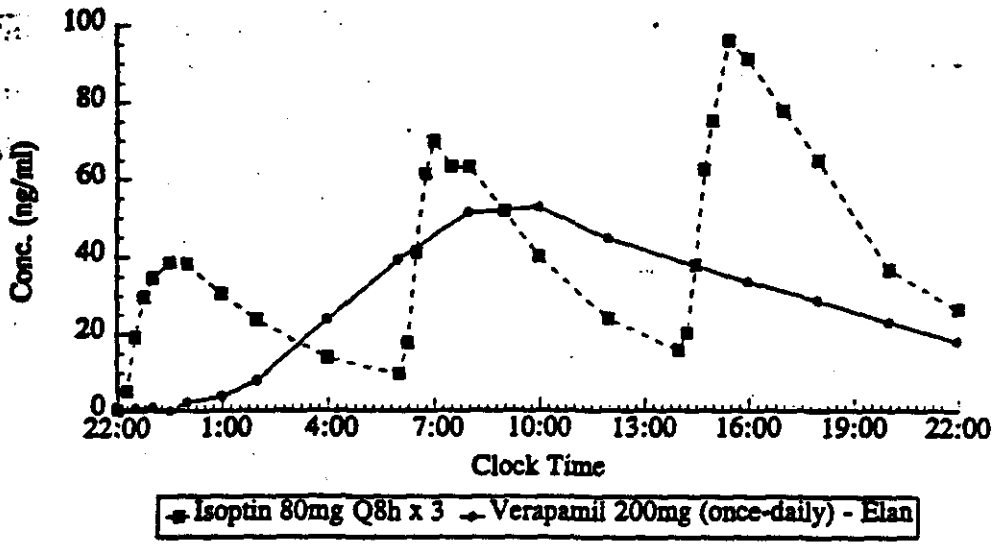
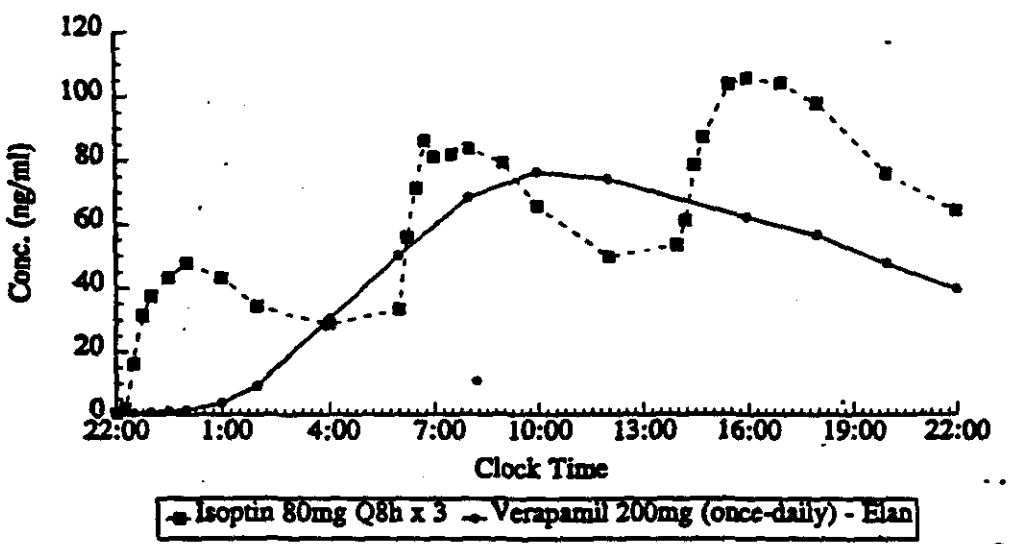


Figure 2

Norverapamil Plasma Concentrations Following PM Dosing

Protocol# 0796006 - Mean Data



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Appendix 2

A single dose study in healthy volunteers to assess the effect of food on the bioavailability of Elan's Verapamil PM 200 mg formulation.

Study No. 0896001 Volume 1.15-19 Pages 1-2353

Study initiated January 27th, 1997
Study completed February 21st, 1997

Investigators:

Objectives:

Primary: To assess the effect of food on the bioavailability of Elan's Verapamil PM 200 mg formulation

Secondary: To monitor the volunteers for adverse events.

Medication:

Verapamil PM 200 mg capsule (single dose) (Elan) Lot # 6H 802 (certificate of analysis provided for review) under fasting conditions. It is assumed that the formulation used is identical to the "to be marketed formulation".

Verapamil PM 200 mg capsule (single dose) (Elan) Lot # 6H 802 (certificate of analysis provided for review) under fed conditions.

Isoptin ® 80 mg tablet (Q8hx3) (Knoll Pharmaceuticals) Lot # 20800056 under fasting conditions.

Dose level:

An oral dose of 200 mg or 240 mg Verapamil in each treatment period.

Study population:

Twenty four male subjects, aged 18-40, 4 of which are non-smokers.

Design:

The study was an open-label, single dose, three treatment, three period, six sequence balanced randomized cross-over study. Subjects were dosed according to a table of randomization prepared with SAS. Each drug was administered with 240 ml of tap water and a mouth check was performed to ensure compliance. On each treatment period of the study, subjects received either an Elan verapamil PM 200 mg capsule or Isoptin® 80 mg 3 times daily at 8 hour intervals. On each treatment period, subjects were requested to fast overnight for 10 hours prior to the first dose. The subjects that were randomized to receive Verapamil PM/fed received a high fat meal 15 minutes prior to dosing. The high fat meal consisted of 2 eggs fried in butter, two slices of buttered toast, 4 ounces of hash browns toasted in butter, two strips of bacon and 8 fluid ounces of whole milk (4000 KJ, 70 g fat). The subjects then remained fasted for 4 hours after dosing. Subjects that randomized to receive Verapamil PM/fasted and Isoptin®, fasted for 10 hours prior to dosing and for 4 hours after dosing. Meal times were: lunch at T_{0+4}, supper at T_{0+12} and dinner at T_{0+18}, where T_0 is the time of the first dose of Isoptin®. The dosing times for Isoptin® were 9 am, 5 pm and 1 am.

Subjects remained sitting or ambulatory for 4 hours after dosing apart from the last dose of Isoptin® when they were allowed to go to bed 1-2 hours after dosing.

Adverse events were recorded.

Venous blood specimens (7 ml) were obtained at the following time points:

Test medication: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36 and 48 hours after dosing.

Reference: pre-dose, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 8.25, 8.5; 8.75, 9, 9.5, 10, 11, 12, 14, 16, 16.25, 16.50, 16.75, 17, 17.5, 18, 19, 20, 22, 24, 30, 36 and 48 hours after dosing.

Samples were collected in EDTA vacutainers and plasma was isolated and frozen at -80 °C.

Assay procedures:

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Data analysis:

Pharmacokinetic parameters were calculated and analyzed as described previously.

Results:

For results on verapamil plasma levels, please refer to tables 3, 5 and 7 attached. For results on norverapamil plasma levels, pelase refer to tables 9, 11 and 13 attached.

The mean Cmax of (±) verapamil for Elan's verapamil PM 200 mg formulation under fasting conditions was 24% less than under fed conditions. This difference was statistically significant. However, the results for (-) verapamil did not show a statistically significant food effect. Even though the AUC (0-48) for (±) verapamil was lower in the fed state, this difference was less than 10% and was considered not to be statistically significant.

For (±) norverapamil, there was a 37% increase in Cmax following administration of the test formulation with food. This increase was statistically significant. However, the slight increase in AUC in the fed compared to the fasting state was considered not to be statistically significant (11 and 7% for AUC(0-48) and AUC(0-inf), respectively.

Table 15. The S/R ratios for both Cmax and AUC for verapamil and norverapamil under fasting and fed conditions were similar. Similarly, there were no differences in the S/R ratio for both Cmax and AUC for Elan's verapamil formulation as compared to

Isoptin, under fasting conditions. Similar results were found with the norverapamil S/R ratios, between Elan and Isoptin formulations under fasting conditions.

Table 16. Under fasting conditions, the relative bioavailability of Elan's verapamil 200mg formulation was 90% compared to Isoptin. However, this bioavailabilty was 108% when dose adjusted to 240 mg. The Cmax for Elan's formulation was, as expected, lower than Isoptin. Similarly, the bioavailability of norverapamil from Elan's formulation was 77% when compared to Isoptin. However, when dose-adjusted to 240 mg, this bioavailability increased to 92%.

Conclusions:

The results show that there was an increase in the rate (Cmax) but not extent (AUC) of absorption of (+) verapamil when Elan's formulation was taken with food. There was however no food effect on the extent or rate of absorption of (-) verapamil.

For norverapamil, food increased the rate but no the extent of absorption for both (+) and (-) norverapamil.

Under fasting conditions, the Cmax for Elan's verapamil (200 mg) was lower than Isoptin (80 mg 3 times a day=240 mg), however the AUCs were comparable when dose adjusted for 240 mg.

Table 3: Mean Non-transformed S-(-) verapamil Pharmacokinetic Parameters#

Mean ± SD, 23 subjects

Parameter	Treatment A Lot No. 6H802 Fasting	Treatment B Lot No. 6H802 Fed	Treatment C Lot No.20800056 Fasting	Ratio B/A
AUC(0-48) ng/ml.h	120.91 ± 86.70	100.37 ± 83.83	130.10 ± 87.49	0.83
Cmax (ng)	9.77 ± 6.42**	11.09 ± 7.45	14.80 ± 8.03	1.14
tmax (h)	8.35 ± 4.85	8.35 ± 3.80	13.28 ± 6.86	1

** Statistically significant difference at P < 0.05, Treatment A vs C comparison

Table 5: Mean Non-transformed R-(+)verapamil Pharmacokinetic Parameters

Mean ± SD, 23 subjects

Parameter	Treatment A Lot No. 6H802 Fasting	Treatment B Lot No. 6H802 Fed	Treatment C Lot No.20800056 Fasting	Ratio B/A
AUC(0-48) ng/ml.h	797.84 ± 357.88	752.57 ± 372.13	950.18 ± 391.29	0.94
AUC(0-infinity) ng/ml.h	862.32 ± 361.04	810.16 ± 382.29	981.48 ± 401.73	0.94
Cmax (ng)	45.51 ± 20.18**	57.59 ± 27.20*	80.15 ± 32.77	1.27
tmax (h)	10.35 ± 3.45	9.30 ± 2.14	11.99 ± 7.43	-
kel (h^{-1})	0.09 ± 0.03	0.11 ± 0.05*	0.14 ± 0.04	-
t½ (h)	8.78 ± 2.67	6.88 ± 2.12*	5.54 ± 2.70	-

* Statistically significant difference at P < 0.05, Treatment A vs B comparison

** Statistically significant difference at P < 0.05, Treatment A vs C comparison

Table 7: Mean Non-transformed (R+S) verapamil Pharmacokinetic Parameters

Mean ± SD, 23 subjects

Parameter	Treatment A Lot No. 6H802 Fasting	Treatment B Lot No. 6H802 Fed	Treatment C Lot No.20800056 Fasting	Ratio B/A
AUC(0-48) ng/ml.h	923.13 ± 442.21	855.34 ± 452.23	1076.17 ± 467.93	0.93
AUC(0-infinity) ng/ml.h	981.11 ± 443.02	908.62 ± 459.49	1102.96 ± 475.08	0.93
Cmax (ng)	55.23 ± 26.38**	68.29 ± 34.31*	94.22 ± 40.11	1.24
tmax (h)	10.43 ± 3.36	9.48 ± 2.02	12.70 ± 7.07	-
kel (h^{-1})	0.09 ± 0.03	0.12 ± 0.05*	0.15 ± 0.05	-
t½ (h)	8.45 ± 2.54 *	6.62 ± 2.06*	5.19 ± 2.71	-

* Statistically significant difference at P < 0.05, Treatment A vs B comparison

** Statistically significant difference at P < 0.05, Treatment A vs C comparison

Table9: Mean Non-transformed S-(-)norverapamil Pharmacokinetic Parameters

Mean ± SD, 21 subjects

Parameter	Treatment A Lot No. 6H802 Fasting	Treatment B Lot No. 6H802 Fed	Treatment C Lot No.20800056 Fasting	Ratio B/A
AUC(0-48) ng/ml.h	301.30 ± 141.65	341.81 ± 154.77	452.17 ± 186.99	1.13
AUC(0-infinity) ng/ml.h	428.11 ± 143.40†	467.41 ± 164.83‡	521.96 ± 199.29	1.09
Cmax (ng)	14.90 ± 6.27**	21.25 ± 9.45*	26.70 ± 8.95	1.43
tmax (h)	14.86 ±3.77	11.14 ± 2.41*	16.37 ± 5.41	-
kel (h^{-1})	0.05 ± 0.02†	0.06 ± 0.04‡	0.08 ± 0.02	-
t½ (h)	15.35 ± 4.60†	14.27 ± 7.92‡	9.85 ± 2.96	-

* Statistically significant difference at P < 0.05, Treatment A vs B comparison

** Statistically significant difference at P < 0.05, Treatment A vs C comparison

Table 11: Mean Non-transformed R-(+)norverapamil Pharmacokinetic Parameters

Mean ± SD, 21subjects

Parameter	Treatment A Lot No. 6H802 Fasting	Treatment B Lot No. 6H802 Fed	Treatment C Lot No.20800056 Fasting	Ratio B/A
AUC(0-48) ng/ml.h	872.69 ± 316.81	967.10 ± 375.24	1213.90 ± 404.62	1.11
AUC(0-infinity) ng/ml.h	1009.97 ± 345.77‡	1079.81 ± 423.54	1321.52 ± 440.99	1.07
Cmax (ng)	37.28 ± 14.26**	50.73 ± 24.16*	62.33 ± 19.35	1.36
tmax (h)	15.62 ± 5.46	12.76 ± 5.78*	16.52 ± 5.39	-
kel (h^{-1})	0.06 ± 0.02‡	0.07 ± 0.03*	0.08 ± 0.02	-
t½ (h)	12.04 ± 3.54‡	10.50 ± 3.28*	9.78 ± 2.47	-

* Statistically significant difference at P < 0.05, Treatment A vs B comparison

** Statistically significant difference at P < 0.05, Treatment A vs C comparison

Table 13: Mean Non-transformed Norverapamil Pharmacokinetic Parameters

Mean ± SD, 21 subjects

Parameter	Treatment A Lot No. 6H802 Fasting	Treatment B Lot No. 6H802 Fed	Treatment C Lot No.20800056 Fasting	Ratio B/A
AUC(0-48) ng/ml.h	1160.86 ± 422.50	1293.67 ± 476.82	1654.99 ± 553.39	1.11
AUC(0-infinity) ng/ml.h	1308.87 ± 505.40†	1401.01 ± 521.26	1777.71 ± 670.18	1.07
Cmax (ng)	51.59 ± 19.59**	70.90 ± 33.27*	87.20 ± 26.93	1.37
tmax (h)	16.00 ± 5.76	11.24 ± 2.05*	16.61 ± 5.38	-
kel (h^{-1})	0.08 ± 0.02†	0.09 ± 0.03*	0.09 ± 0.03	-
½ (h)	9.50 ± 2.11†	9.10 ± 4.86	8.03 ± 2.15	-

Statistically significant difference at P < 0.05, Treatment A vs B comparison

** Statistically significant difference at P < 0.05, Treatment A vs C comparison

Table 15: Mean verapamil and norverapamil S/R ratios

Parameter	Verapamil PM Fasted S/R Ratio	Verapamil PM Fed S/R Ratio	Isoptin Fasted S/R Ratio
	Verapamil		
AUC(0-48)	0.13 ± 0.07	0.11 ± 0.07	0.12 ± 0.06
AUC(0-inf)	-	-	-
Cmax	0.19 ± 0.09	0.17 ± 0.08	0.17 ± 0.06
	Norverapamil		
AUC(0-48)	0.34 ± 0.12	0.35 ± 0.14	0.36 ± 0.10
AUC(0-inf)	0.42 ± 0.07	0.47 ± 0.20	0.39 ± 0.07
Cmax	0.41 ± 0.15	0.42 ± 0.08	0.44 ± 0.17

Table 16 Relative bioavailability of verapamil and norverapamil

Treatment A/C

Parameter	S-(-)enantiomer	R-(+) enantiomer	R+S
	Verapamil		
F	0.91 ± 0.50†	0.89 ± 0.19	0.90 ± 0.20
F(dose adjusted	1.09 ± 0.60†	1.07 ± 0.23	1.08 ± 0.24
	Norverapamil		
F	0.86 ± 0.19	0.77 ± 0.22	0.77 ± 0.23
F(dose adjusted	1.03 ± 0.23	0.92 ± 0.26	0.92 ± 0.28

† Calculated from $AUC_{(0-48)}$

Appendix 3

A steady state study in healthy male volunteers to evaluate the Bioavailability of Elan's verapamil PM 200 mg formulation following night time dosing relative to Isoptin® 80 mg tablet (Knoll Pharmaceuticals) three times daily at eight hours interval.

Study No. 0896002 Volume 1.20-25 Pages 1-2651

Study initiated March 6th, 1997
Study completed April 24th, 1997

Investigators:

Objectives:

Primary: To evaluate the bioavailability of Elan's Verapamil PM 200 mg formulation at steady state relative to Isoptin® 80 mg tablet (Knoll Pharmaceuticals) dosed three times daily at 8 hourly intervals with both medications dosed at night.

Secondary: To monitor the volunteers for adverse events.

Medication:

Verapamil PM 200 mg capsule (single dose) (Elan) Lot # 6H 802 (certificate of analysis provided for review) under fasting conditions for 5 days. It is assumed that the formulation used is identical to the "to be marketed formulation". The subjects were dosed at 10:00 pm (time 0).

Isoptin ® 80 mg tablet (Q8hx3) (Knoll Pharmaceuticals) Lot # 20800056 under fasting conditions for 5 days. The subjects were dosed at 10:00 pm (T 0), then T 0+8 and T 0+16.

Dose level:

An oral dose of 200 mg or 240 mg Verapamil on each of Days 1-5 in each treatment period.

Study population:

Twenty four male subjects, aged 18-40, 4 of which are non-smokers.

Design:

The study was an open-label, two treatment, two period, multiple dose, balanced randomized cross-over study with up to a seven day washout between treatment periods.

Subjects were dosed according to a table of randomization prepared with SAS. Each drug was administered with 240 ml of tap water and a mouth check was performed to ensure compliance.

Subjects randomized to receive the 200 mg verapamil PM formulation were fasted 4 hours prior to dosing on each of days 1-5 and remained fasting for 10 hours after dosing. Subjects were dosed while standing.

Adverse events were recorded.

Plasma levels of verapamil, norverapamil and their enantiomers were measured by blood sampling (7 ml) at:

Day 1-4: 0 hours
Day 5: 0 hours (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36 and 48 hours after dosing with verapamil PM and by sampling at:

Day 1-4: 0 hours
Day 5: 0 hours (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 8.25, 8.5, 8.75, 9, 9.5, 10, 11, 12, 14, 16, 16.25, 16.5, 16.75, 17, 17.5, 18, 19, 20, 22, 24, 30, 36 and 48 hours after dosing with Isoptin®.

Samples were collected in EDTA vacutainers and plasma was isolated and frozen at -80 °C.

Assay procedures:

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Data analysis:

Pharmacokinetic parameters were calculated and analyzed as described previously. Briefly, attainment of steady state was determined for each subject by linear regression analysis using procedure of SAS. An ANOVA was performed on the PK parameters with the following sources of variation included in the model: sequence, subjects, subjects nested in sequences, period and treatment. Tmax and tmin were analyzed using the Wilcoxon option of SAS.

90% confidence intervals were calculated using least squares mean values for the treatments. The %Cv for AUC_{ss} (0-24) and $Cmax_{ss}$ was estimated as a measure of intersubject variability.

To determine that steady state had been achieved, linear regression analysis through the pooled and individual plasma concentrations at the times 48, 72 and 96 hours for (±) verapamil and norverapamil of both treatments (verapamil PM and Isoptin) was performed. These determinations were made at trough levels of verapamil since on days 1-4, sampling was only done at time zero (pre-dose). A subject was determined to be at steady state if the slope of the line through those three points was not significantly different from zero.

Results:

Determination of steady state: linear regression analysis through the pooled and individual plasma concentrations at 48, 72 and 96 hours data for (±) verapamil and (±) norverapamil for both treatments (verapamil PM and Isoptin®) were not significantly different from zero. This indicated that most subjects were at steady state by day 5. Occasionally, individual subjects did not reach steady state, however, that data did not affect the overall steady state determinations.

No sequence or period effects were observed for verapamil or norverapamil.

Figures 1 and 2 show the concentration time profiles for day 5. Tables 4, 6 and 8 show the calculated PK parameters for verapamil whereas tables 10, 12 and 14 show the calculated PK parameters for norverapamil.

As expected, the mean Cmax and AUC for verapamil and norverapamil for Elan's formulation were lower than those for Isoptin®. Clearly Isoptin® was administered at a higher dose (240 mg versus 200 mg) and this latter finding was to be expected. The relative dose-adjusted bioavailability of verapamil PM to Isoptin® was 83% for both verapamil and norverapamil.

Table 8 shows that significant differences in the peak-to-trough fluctuation index were noted between the 2 formulations, with Elan's formulation having a lower fluctuation index. However, for norverapamil, no significant difference in the fluctuation index was noted between Elan's formulation and Isoptin®.

S/R ratios for verapamil did not show differences in Cmax, whereas a significant difference in AUC was noted (table 15). For norverapamil, neither Cmax nor AUC exhibited difference in the S/R ratios for the 2 treatments.

Conclusions:

The data show that following a 5-day administration of Elan's 200 mg verapamil PM, steady state is achieved. Additionally, a lag time of 4 hours is observed, giving rise to therapeutic levels of verapamil approximately 6-8 hours after doing. This would provide maximum exposure in the morning hours, assuming that verapamil PM is taken at bedtime (Figures 1 and 2).

The overall exposure of Elan's verapamil was lower than Isoptin® (Table 8 and 14, adjusted Fss).

Elan's formulation achieved lower peak to trough fluctuations, as measured by (Cmax-Cmin)/Cav, as compared to Isoptin®. It is stated that the significantly lower lower peak to trough fluctuations should ensure the safety of the product.

The dose-adjusted bioavailability of verapamil was similar at steady state, as compared to the that at single dose ($F=87\%\pm19\%$ and $F_{ss}=83\%\pm16\%$). Similarly, Cav was similar at steady state to Cmax in the single dose study ($Cav=51.31\pm28.54$ ng/ml and Cmax (after a single dose)$= 56.43\pm24.98$ ng/ml). For norverapamil, $C_{ave}=66.84$ ng/ml at steady state, whereas Cmax after a single dose$=81.92$ ng/ml.

Table 4. Mean Non-transformed Steady State Pharmacokinetic Parameters

(Mean ± SD) S-(-) Verapamil

Parameter	Treatment A Lot 66H802	Treatment B Lot 20800056	Statistical Analysis (90% C.I).
AUC_{ss} (0-24h)	194.92 ± 151.65	295.96 ± 186.53*	57.94 - 73.79
$Cmax_{ss}$	16.83 ± 10.75	26.84 ± 15.43*	51.50 - 73.95
$tmax_{ss}$	10.92 ± 2.89	13.52 ± 4.36*	-
$Cmin_{ss}$	2.02 ± 3.26	2.92 ± 4.01*	47.55 - 90.68
tmin	0.60 ± 1.03	3.56 ± 6.23*	-
$Cmax_{ss}$ - $Cmin_{ss}$	14.82 ± 7.98	23.92 ± 12.48*	49.52 - 74.37
‡$Cmax_{ss}/Cmin_{ss}$	4.54 ± 0.72	5.26 ± 1.53	56.84 - 96.78
Cav (0-24h)	8.12 ± 6.32	12.33 ± 7.77*	57.94 - 73.79
$Cmax_{ss}$/C24h	3.02 ± 0.62	3.53 ± 0.88	66.37 - 94.41
‡($Cmax_{ss}$ - $Cmin_{ss}$)/$Cmin_{ss}$	3.54 ± 0.72	4.26 ± 1.53	46.26 - 95.99
($Cmax_{ss}$ - $Cmin_{ss}$)/Cav	2.73 ± 2.24†	2.26 ± 0.80	95.03 - 155.56
Fss F(adjusted)	0.59 ± 0.25 0.71 ± 0.30	-	-

† 23 subjects

‡ 7 & 9 subjects for treatments A & B respectively

* p≤0.05 Statistically significant difference between treatments A & B.

Table 6. Mean Non-transformed Steady State Pharmacokinetic Parameters

(Mean ± SD) Mean. 24 subjects R-(+) Verapamil

Parameter	Treatment A Lot 6H802	Treatment B Lot 20800056	Statistical Analysis (90% C.I).
AUC_{ss} (0-24h)	1036.63 ± 534.82	1459.23 ± 694.06*	65.10 - 76.98
$Cmax_{ss}$	77.77 ± 39.97	124.18 ± 57.56*	53.92 - 71.33
$tmax_{ss}$	10.58 ± 2.08	11.82 ± 4.20	-
$Cmin_{ss}$	16.02 ± 11.57	22.83 ± 13.70*	61.38 - 78.91
tmin	4.13 ± 7.72	9.06 ± 8.41*	-
$Cmax_{ss}$ - $Cmin_{ss}$	61.76 ± 30.41	101.35 ± 46.96*	50.60 - 71.27
$Cmax_{ss}/Cmin_{ss}$	5.24 ± 1.83‡	5.71 ± 1.94†	80.95 - 109.76
Cav (0-24h)	43.19 ± 22.28	60.80 ± 28.92*	65.10 - 76.98
$Cmax_{ss}$/C24h	4.07 ± 1.59†	4.06 ± 1.22	88.48 - 113.79
($Cmax_{ss}$ - $Cmin_{ss}$)/$Cmin_{ss}$	4.24 ± 1.83‡	4.71 ± 1.94†	76.88 - 111.85
($Cmax_{ss}$ - $Cmin_{ss}$)/Cav	1.49 ± 0.29	1.70 ± 0.29*	80.63 - 94.64
Fss F(adjusted)	0.70 ± 0.11 0.84 ± 0.13	-	-

† 23 subjects

‡ 22 subjects

* p≤0.05 Statistically significant difference between treatments A & B.

Table 8. Mean Non-transformed Steady State Pharmacokinetic Parameters

(Mean ± SD) Mean. 24 subjects (R+S) Verapamil

Parameter	Treatment A Lot 6H802	Treatment B Lot 20800056	Statistical Analysis (90% C.I).
AUC_{ss} (0-24h)	1231.33 ± 684.97	1755.57 ± 878.43*	63.93 - 76.35
$Cmax_{ss}$	94.51 ± 50.59	149.70 ± 72.45*	54.15 - 72.12
$tmax_{ss}$	10.83 ± 1.86	12.24 ± 4.20	-
$Cmin_{ss}$	18.05 ± 14.59	26.06 ± 17.20*	60.55 - 77.97
tmin	4.13 ± 7.72	8.75 ± 8.59	-
$Cmax_{ss}$ - $Cmin_{ss}$	76.46 ± 38.00	123.63 ± 58.69*	51.41 - 72.27
$Cmax_{ss}/Cmin_{ss}$	6.03 ± 2.37‡	6.14 ± 1.84†	90.82 - 113.46
Cav (0-24h)	51.31 ± 28.54†	73.15 ± 36.60*	63.93 - 76.35
$Cmax_{ss}$/C24h	4.54 ± 2.04	4.35± 1.56	91.19 - 119.87
($Cmax_{ss}$ - $Cmin_{ss}$)/$Cmin_{ss}$	5.03 ± 2.37‡	5.14 ± 1.84†	89.03 - 116.09
($Cmax_{ss}$ - $Cmin_{ss}$)/Cav	1.58 ± 0.31	1.73 ± 0.28*	84.88 - 97.73
Fss F(adjusted)	0.69 ± 0.13 0.83 ± 0.16	-	-

† 23 subjects

Table 10. Mean Non-transformed Steady State Pharmacokinetic Parameters

(Mean ± SD) Mean. 23 subjects S-(-) Nonverapamil

Parameter	Treatment A Lot 6H802	Treatment B Lot 20800056	Statistical Analysis (90% C.I).
AUC_{ss} (0-24h)	487.45 ± 195.53	706.91 ± 261.34*	63.74 - 73.92
$Cmax_{ss}$	31.98 ± 13.04	42.54 ± 13.60*	68.83 - 80.95
$tmax_{ss}$	11.83 ± 2.17	2.57 ± 0.99*	-
$Cmin_{ss}$	8.87 ± 6.08	13.67 ± 9.40*	36.08 - 93.58
tmin	2.59 ± 2.59	5.58 ± 5.59*	-
$Cmax_{ss}$ - $Cmin_{ss}$	23.11 ± 11.39	28.87 ± 10.00*	66.72 - 92.56
†$Cmax_{ss}/Cmin_{ss}$	3.49 ± 1.81	2.83 ± 0.75	100.77 - 161.33
Cav (0-24h)	20.31 ± 8.15	29.45 ± 10.89*	63.74 - 73.92
‡$Cmax_{ss}$/C24h	2.24 ± 0.59	1.74 ± 0.27*	116.04 - 141.29
†($Cmax_{ss}$ - $Cmin_{ss}$)/$Cmin_{ss}$	2.49 ± 1.81	1.83 ± 0.75	101.23 - 197.80
($Cmax_{ss}$ - $Cmin_{ss}$)/Cav	1.15 ± 0.31	1.03 ± 0.30	98.19 - 125.67
Fss	0.69 ± 0.10	-	-
F(adjusted)	0.83 ± 0.12		

† 19 subjects

‡ 22 subjects

* p≤0.05 Statistically significant difference between treatments A & B.

Table 12. Mean Non-transformed Steady State Pharmacokinetic Parameters

(Mean ± SD) R(+) Nonverapamil

Parameter	Treatment A Lot 6H802	Treatment B Lot 20800056	Statistical Analysis (90% C.I).
AUC_{ss} (0-24h)	1132.20 ± 414.62	1605.90 ± 558.34*	65.79 - 75.01
$Cmax_{ss}$	71.36 ± 26.13	98.83 ± 32.04*	63.76 - 80.05
$tmax_{ss}$	11.30 ± 2.22	10.67 ± 4.53	-
$Cmin_{ss}$	21.58 ± 13.45	32.14 ± 19.63*	44.38 - 90.09
tmin	2.80 ± 4.91	6.89 ± 7.01	-
$Cmax_{ss}$ - $Cmin_{ss}$	49.79 ± 23.09	66.69 ± 23.98*	59.77 - 88.50
$Cmax_{ss}/Cmin_{ss}$	3.76 ± 2.01‡	3.03 ± 1.04†	99.29 - 159.80
Cav (0-24h)	47.18 ± 17.28	66.91 ± 23.26*	65.79 - 75.01
$Cmax_{ss}$/C24h	2.28 ± 0.54	1.89 ± 0.63*	105.18 - 135.57
($Cmax_{ss}$ - $Cmin_{ss}$)/$Cmin_{ss}$	2.76 ± 2.01‡	2.03 ± 1.04†	98.91 - 191.52
($Cmax_{ss}$ - $Cmin_{ss}$)/Cav	1.06 ± 0.25	1.06 ± 0.44	82.71 - 116.05
Fss	0.70 ± 0.08	-	-
F(adjusted)	0.84 ± 0.10		

† 20 subjects

‡ 22 subjects

* p≤0.05 Statistically significant difference between treatments A & B.

Table 14. Mean Non-transformed Steady State Pharmacokinetic Parameters

(Mean ± SD) (R+S) Nonverapamil

Parameter	Treatment A Lot 6H802	Treatment B Lot 20800056	Statistical Analysis (90% C.I).
AUC_{ss} (0-24h)	1604.18 ± 615.59	2307.37 ± 812.72*	64.65 - 74.15
$Cmax_{ss}$	100.59 ± 38.36	140.48 ± 42.91*	64.39 - 78.31
$tmax_{ss}$	11.57 ± 2.33	11.39 ± 4.29	-
$Cmin_{ss}$	31.29 ± 18.75	46.71 ± 28.25*	42.86 - 91.21
tmin	3.89 ± 6.54	6.70 ± 7.39	-
$Cmax_{ss}$ - $Cmin_{ss}$	69.30 ± 34.48	93.77 ± 30.78*	60.18 - 86.78
$max_{ss}/Cmin_{ss}$	3.71 ± 2.23‡	2.96 ± 0.96†	100.31 - 165.25
v (0-24h)	66.84 ± 25.65	96.14 ± 33.86*	64.65 - 74.15
$Cmax_{ss}$/C24h	2.22 ± 0.50	1.80 ± 0.49*	109.92 - 136.54
($Cmax_{ss}$ - $Cmin_{ss}$)/$Cmin_{ss}$	2.71 ± 2.23‡	1.96 ± 0.96†	100.48 - 202.07
($Cmax_{ss}$ - $Cmin_{ss}$)/Cav	1.03 ± 0.25	1.03 ± 0.39	83.93 - 115.05
Fss	0.69 ± 0.09	-	-
F(adjusted)	0.83 ± 0.11		

† 20 subjects

Table 15 Mean verapamil and norverapamil S/R ratios (Mean ± SD), 24 subjects

Parameter	S/R Ratio	
	Treatment A Lot 6H802	Treatment B† Lot 20800056
	Verapamil	
AUCss	0.16 ± 0.07	0.19 ± 0.05*
Cmaxss	0.20 ± 0.05	0.21 ± 0.03
	Norverapamil	
AUCss	0.43 ± 0.06	0.44 ± 0.05
Cmaxss	0.45 ± 0.12	0.44 ± 0.08

† 23 subjects

* $p \leq 0.05$ Statistically significant difference between treatments A & B.

Figure 1a

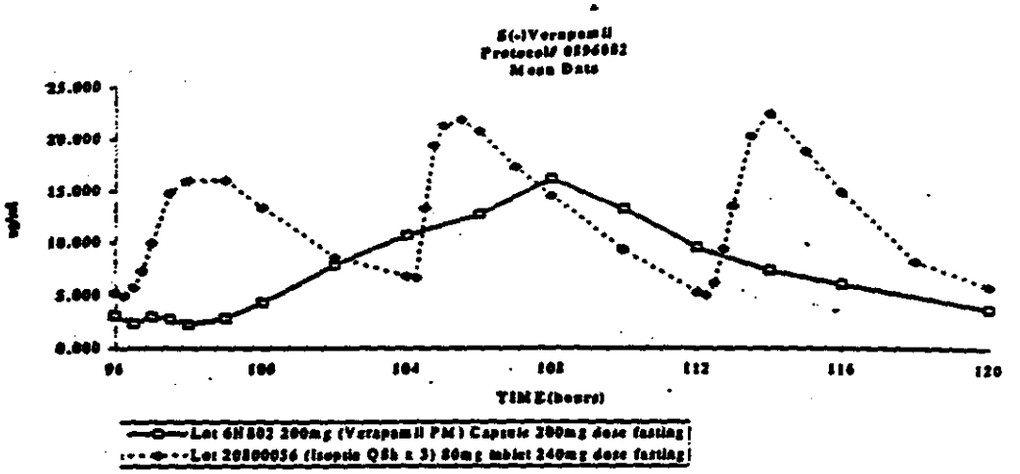

Figure 1b

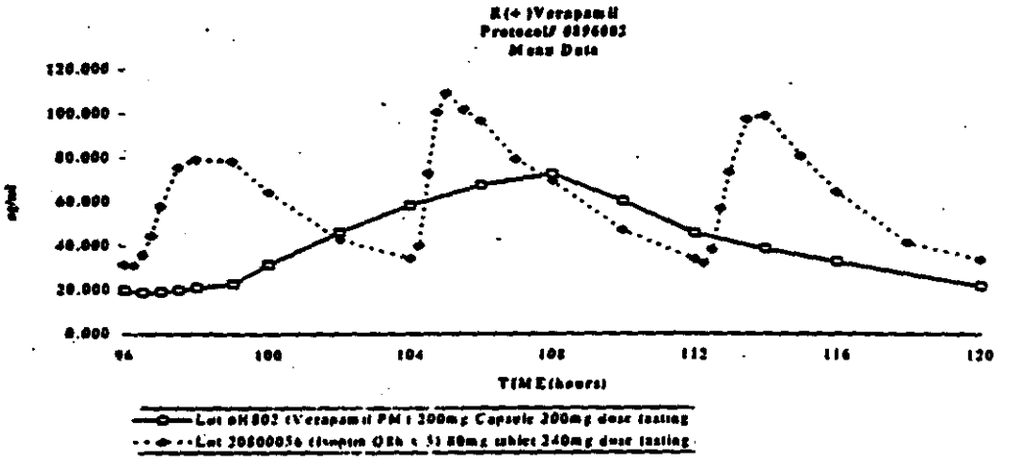

Figure 1c

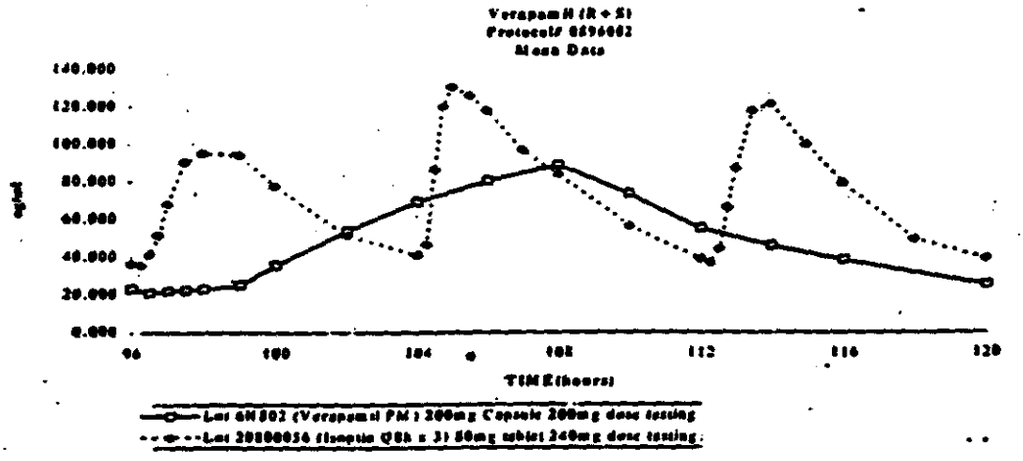

Fig
Table 2a

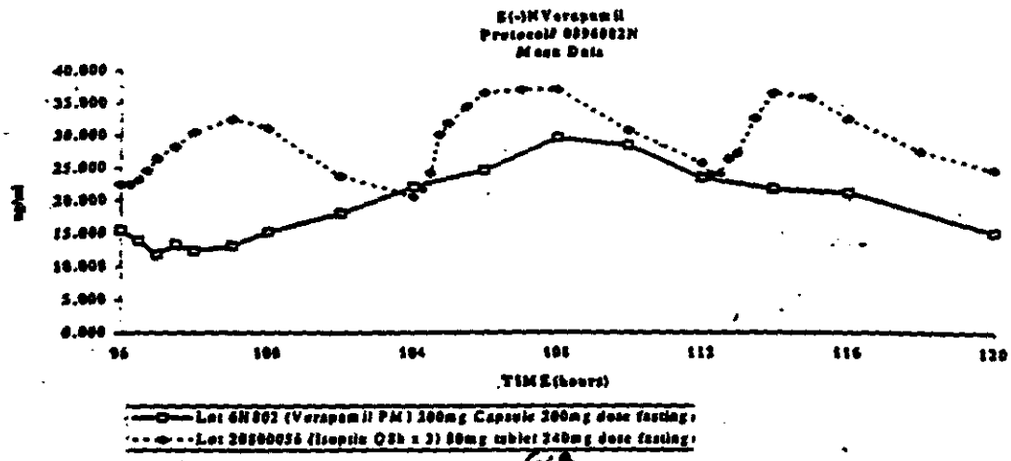

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Table 2b

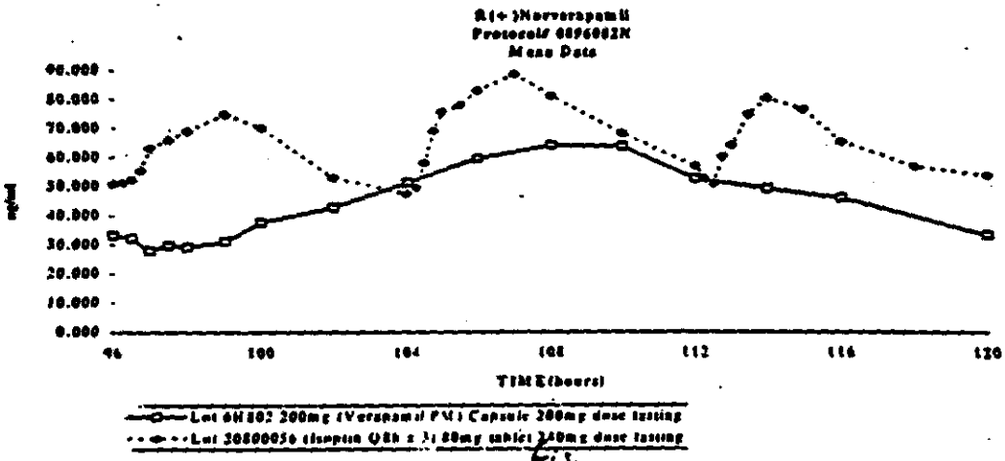

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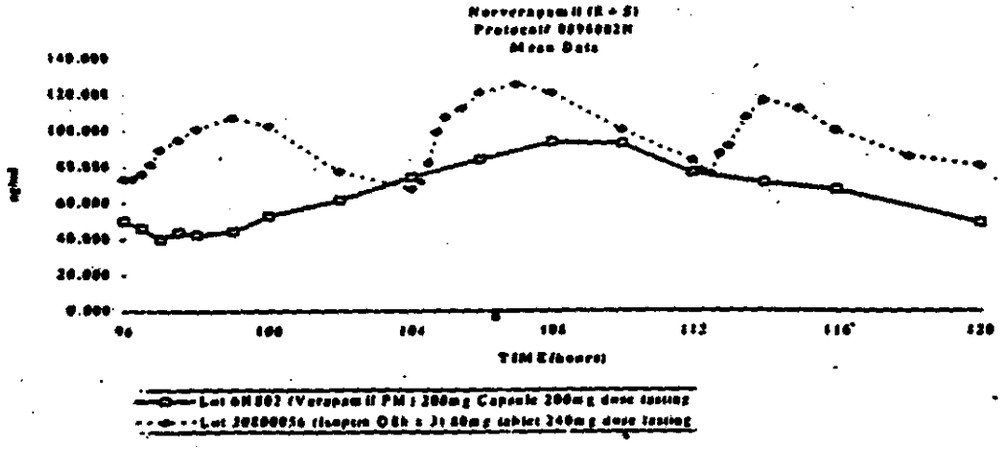
Table 2c



Appendix 4

A single dose study in healthy volunteers to evaluate the dose proportionality of the Elan verapamil formulation following night time administration of 100, 200, 300 and 400 mg doses.

Study No. 0197005 Volume 1.26-32 Pages 1-2733

Study initiated May 29th, 1997
Study completed July 5th, 1997

Investigators:

Objectives:

Primary: To evaluate dose proportionality of the Elan Verapamil PM formulation following night time administration at 100, 200, 300 and 400 mg doses.

Secondary: To monitor the volunteers for adverse events.

Medication:

Treatment A: Verapamil PM 100 mg capsule (single dose) (Elan) Lot # 7C 807 (certificate of analysis provided for review) under fasting conditions.

Treatment B: Verapamil PM 200 mg capsule (single dose) (Elan) Lot # 7C 805 (certificate of analysis provided for review) under fasting conditions.

Treatment C: Verapamil PM 300 mg capsule (single dose) (Elan) Lot # 7C 806 (certificate of analysis provided for review) under fasting conditions.

Treatment D: Verapamil PM 400 mg (2x200 mg capsule) under fasting conditions.

Dose level:

A total oral dose of 100, 200, 300 and 400 mg Verapamil in each treatment period.

Study population:

Twenty four male subjects, aged 18-40. Twenty eight subjects entered the study in order to ensure that 24 will complete the study.

Design:

The study was an open-label, four treatment, four period, balanced, rising dose-cross-over study with at least a seven day washout between treatment periods. Randomization will be applied to study entry. Doses will be administered sequentially starting at the 100 mg strength and increasing to the next highest level.

Each dose was administered with 240 ml of tap water and a mouth check was performed to ensure compliance. Subjects were dosed while standing and were requested to remain sitting or ambulatory for two hours after dosing and supine for a further 8 hours. Subjects were requested to fast for 4 hours prior to dosing and for 10 hours after dosing. Dosing will be between 9-11 pm. A light breakfast will be given 10 hours after dosing, lunch 14 hours after doing and dinner 18 hours after dosing.

Adverse events were recorded.

Plasma levels of verapamil, norverapamil and their enantiomers were measured by blood sampling (7 ml) at:

> 0 hours (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36 and 48 hours after dosing with verapamil PM.

Samples were collected in EDTA vacutainers and plasma was isolated and frozen at -80 °C.

Assay procedures:

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Data analysis:

Pharmacokinetic parameters were calculated and analyzed as described previously.

An ANOVA was performed on the PK parameters using procedures of SAS.

90% confidence intervals were calculated using least squares mean values for the treatments.

ANOVA and 90% confidence interval estimation was also conducted on AUC (0-48 hr), AUC (0-inf) and Cmax dose-normalized data transformed to log base 10.

Results:

Please note that the plasma concentrations of (S)-verapamil following administration of a 100 mg dose were below the limit of quantitation and were therefore not included in the statistical analysis.

The following table represents the mean non-transformed pharmacokinetic parameters for verapamil and norverapamil:

Parameter	100mg	200mg	300mg	400mg
		(S)-verapamil		
AUC (inf)	below LOQ	200.76±102.95	270.97±117.23	441.78±213.77
Cmax	below LOQ	8.99±5.72	16.95±7.20	22.55±11.34
		(R)-verapamil		
AUC(inf)	274.37±146.50	822.98±368.05	1373.28±455.16	1931.46±711.00
Cmax	16.13±5.58	43.89±21.51	83.13±30.13	102.88±39.68
		(S)-norverapamil		
AUC (inf)	306.63±.12	569.81±257.89	723.76±189.14	1002.27±283.80
Cmax	9.09±6.80	18.13±6.16	30.70±10.40	37.99±12.31
		(R)-norverapamil		
AUC (inf)	584.33±257.49	1175.95±367.34	1668.02±386.40	2332.07±657.20
Cmax	18.83±5.81	44.38±16.84	72.32±26.20	88.63±29.00

The following is a table of the mean dose-normalized log10-transformed geometric means of the PK parameters:

Parameter	100mg	200mg	300mg	400mg
		(S)-verapamil		
AUC (inf)	below LOQ	359.70±1.61	328.43±1.58	383.32±1.80
Cmax	below LOQ	18.79±1.53	20.96±1.48	20.26±1.61
		(R)-verapamil		
AUC(inf)	999.54±1.52	1494.67±1.57	1735.59±1.40	1808.25±1.45
Cmax	60.90±1.42	79.11±1.59	105.07±1.38	96.87±1.41
		(S)-norverapamil		
AUC (inf)	1047.85±1.73	1046.59±1.51	934.49±1.30	962.40±1.35
Cmax	37.26±1.55	34.18±1.44	38.84±1.39	36.09±1.39
		(R)-norverapamil		
AUC (inf)	2034.80±1.45	2258.84±1.33	2168.61±1.26	2243.33±1.33
Cmax	72.37±1.33	83.54±1.42	91.36±1.39	84.54±1.36

For statistical analysis and 90% confidence intervals for dose-normalized AUC and Cmax, as well as for mean verapamil and norverapamil S/R ratios, please refer to tables provided in this appendix. Additionally, for graphical representation of the data, please refer to figures provided in this appendix.

A dose-proportional increase in the Cmax and AUC(inf) of (S)-verapamil was noted in the 200-400 mg range. No statistically significant differences in the dose-normalized data were noted, however, bioequivalence was not achieved between the doses of (S)-verapamil.

For (R)-verapamil, statistically significant differences in the Cmax and AUC(inf) of the dose-normalized data was seen between 100 mg and 200, 300 and 400 mg doses. Additionally, Cmax of (R)-verapamil at the 200 mg was significantly different from the 300mg dose. Dose-proportional increases in the AUC(inf) were observed in the 200-400 mg dose range, however, bioequivalence was not achieved.

Ratios of S/R verpamil for Cmax and AUC were comparable across the 200-400 mg dose range.

For (R) and (S)-norverapamil, dose-proportionate increases in Cmax and AUC(inf) were noted over the entire dose range. No statistically significant differences in the dose-normalized data were observed, except for (R)-norverapamil between the 200 and 300 mg dose.

The following is a table of the ratios of the AUCs and Cmaxs dose-normalized to 100 mg. Please note that for (S)-verapamil, the data are dose-normalized to 200 mg, since the values for AUC and Cmax were below the detection limit at the 100 mg dose.

Parameter	100 mg	200 mg	300 mg	400 mg
(S)-verapamil				
AUC (inf)	below LOQ	-	1.35	2.2
Cmax	below LOQ	-	1.88	2.5
(R)-verapamil				
AUC(inf)	-	3	5.0	7.0
Cmax	-	2.72	5.15	6.4
(S)-norverapamil				
AUC (inf)	-	1.86	2.36	3.27
Cmax	-	1.99	3.38	4.18
(R)-norverapamil				
AUC (inf)	-	2.01	2.85	3.99
Cmax	-	2.36	3.84	4.71

Conclusions:

The sponsor concludes that there is evidence for dose proportionality for AUC and Cmax of (S)-verapamil in the 200-400 mg range and for (R)-verapamil in the 300-400 mg range. This has led the sponsor to conclude that some degree of linearity exists for verapamil. For norverapamil, dose linarity was seen over the 100-400 mg range for AUC(inf) and Cmax of both enantiomers, except for the 100-200 mg range of (R)-norverapmil.

Reviewer's comments: Despite the sponsor's efforts to claim that a dose-proportionate linear relationship exists in the pharmacokinetic parameters of verapamil, it appears that such a conclusion was not reached by the data. Additionally, it has been reported previously for verapamil (Calan SR package insert) that a non-linear correlation exists between verapamil dose and plasma concentrations. However, over limited dose ranges, there appears to be some degree of dose-proportionality for verapamil and certainly norverapamil.

Statistical analysis and 90% Confidence Intervals for Dose-Normalized

Parameter	Comparison	90% Confidence Interval	
		Verapamil	Norverapamil
	S-enantiomer		
AUC(inf)	100mg vs 200mg dose	-	81.09 - 123.61
	100mg vs 300mg dose	-	90.82 - 138.44
	100mg vs 400mg dose	-	88.33 - 134.20
	200mg vs 300mg dose	80.95 - 148.17	93.23 - 134.54
	200mg vs 400mg dose	69.36 - 126.95	90.70 - 130.38
	300mg vs 400mg dose	66.03 - 111.18	80.99 - 116.42
Cmax	100mg vs 200mg dose	-	90.90 - 130.75
	100mg vs 300mg dose	-	79.98 - 115.05
	100mg vs 400mg dose	-	86.08 - 123.83
	200mg vs 300mg dose	72.31 - 111.18	73.82 - 104.88
	200mg vs 400mg dose	74.83 - 115.05	79.45 - 112.89
	300mg vs 400mg dose	84.07 - 127.39	90.30 - 128.30
	R-enantiomer		
AUC(inf)	100mg vs 200mg dose	55.00 - 81.32 *	77.75 - 104.37
	100mg vs 300mg dose	47.36 - 70.03 *	80.85 - 108.89
	100mg vs 400mg dose	45.46 - 67.22 *	78.29 - 105.09
	200mg vs 300mg dose	71.13 - 104.27	89.90 - 120.68
	200mg vs 400mg dose	68.27 - 100.08	87.05 - 116.47
	300mg vs 400mg dose	79.27 - 116.21	83.43 - 112.00
Cmax	100mg vs 200mg dose	64.31 - 92.16 *	73.98 - 101.42
	100mg vs 300mg dose	48.42 - 69.39 *	67.65 - 92.74
	100mg vs 400mg dose	52.52 - 75.26 *	73.11 - 100.23
	200mg vs 300mg dose	62.89 - 90.14 *	78.24 - 106.88 *
	200mg vs 400mg dose	68.22 - 97.77	84.55 - 115.50
	300mg vs 400mg dose	90.60 - 129.85	92.46 - 126.31

*Statistically Significant.

Parameter	Treatment A Lot No. 7C807	Treatment B Lot No. 7C805	Treatment C Lot No.7C806	Treatment D Lot No.7C805
	Verapamil ratios (S/R)			
Cmax	-	0.19 ± 0.09	0.20 ± 0.03	0.21 ± 0.04
AUC(inf)	-	0.19 ± 0.09	0.19 ± 0.05	0.21 ± 0.05
	Norverapamil ratios (S/R)			
Cmax	0.41 ± 0.23	0.41 ± 0.08	0.42 ± 0.06	0.42 ± 0.05
AUC(inf)	0.50 ± 0.24	0.47 ± 0.13	0.43 ± 0.05	0.43 ± 0.06

Figure 1a

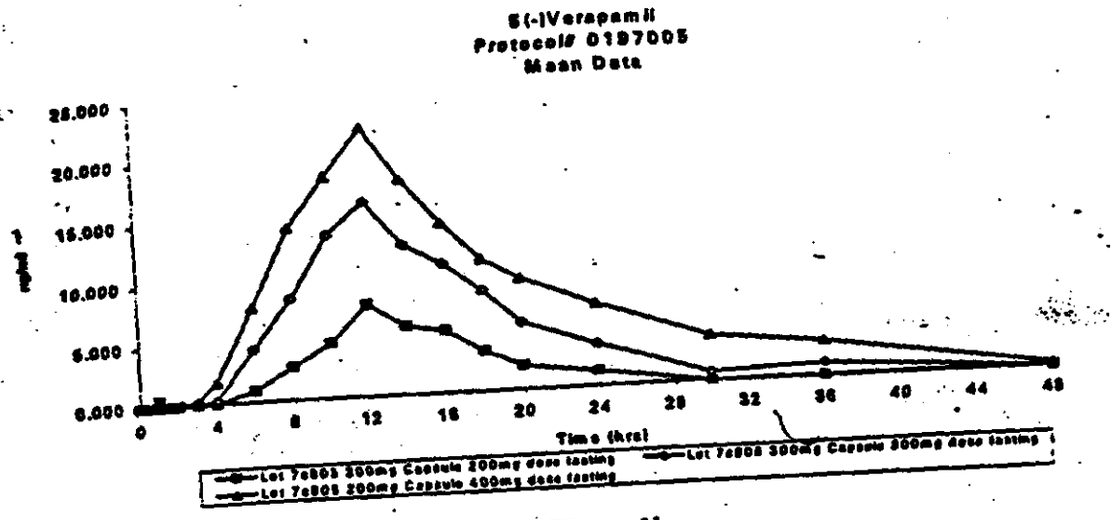


Figure 1b

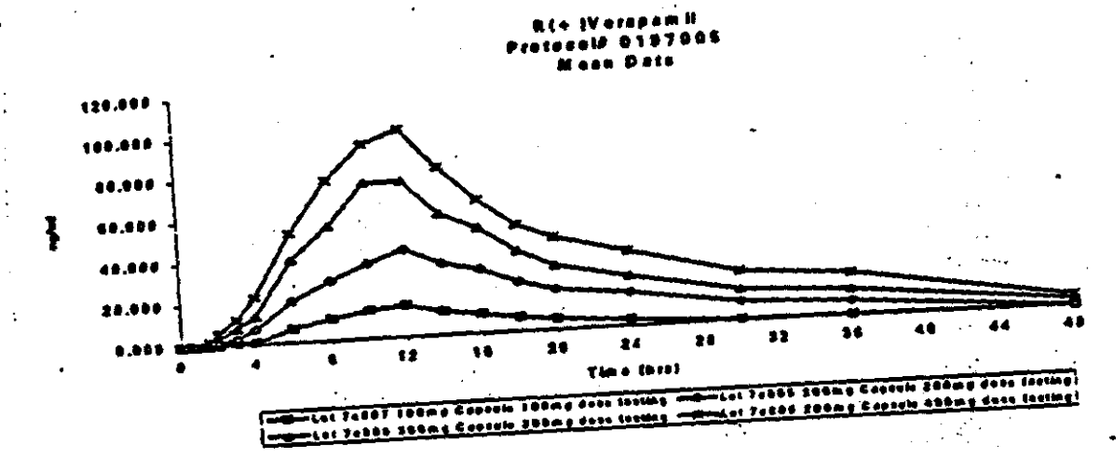


Figure 1c

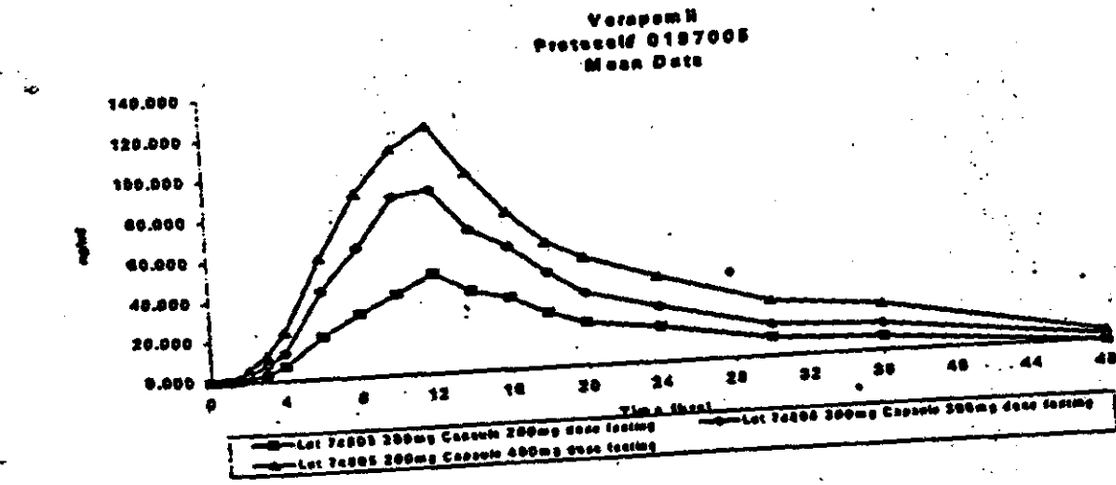


Figure 2a

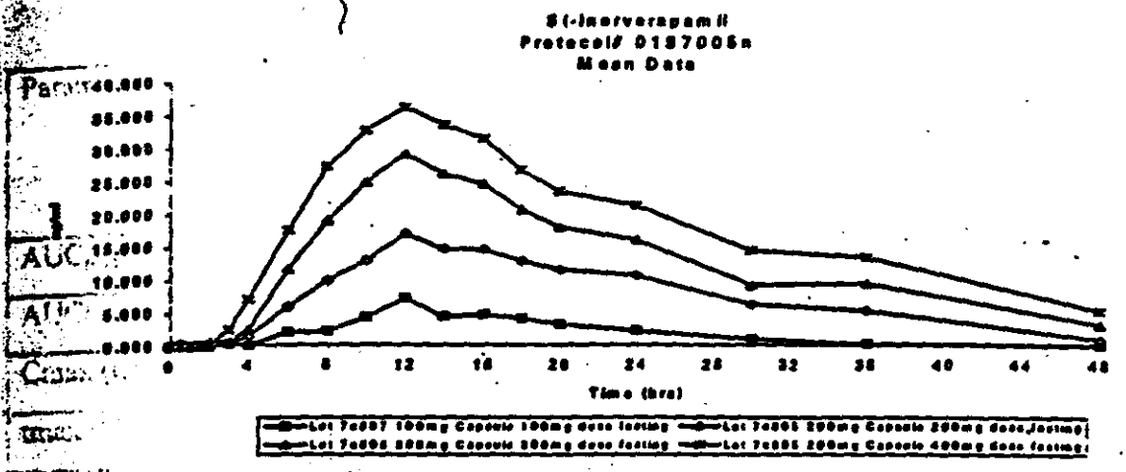
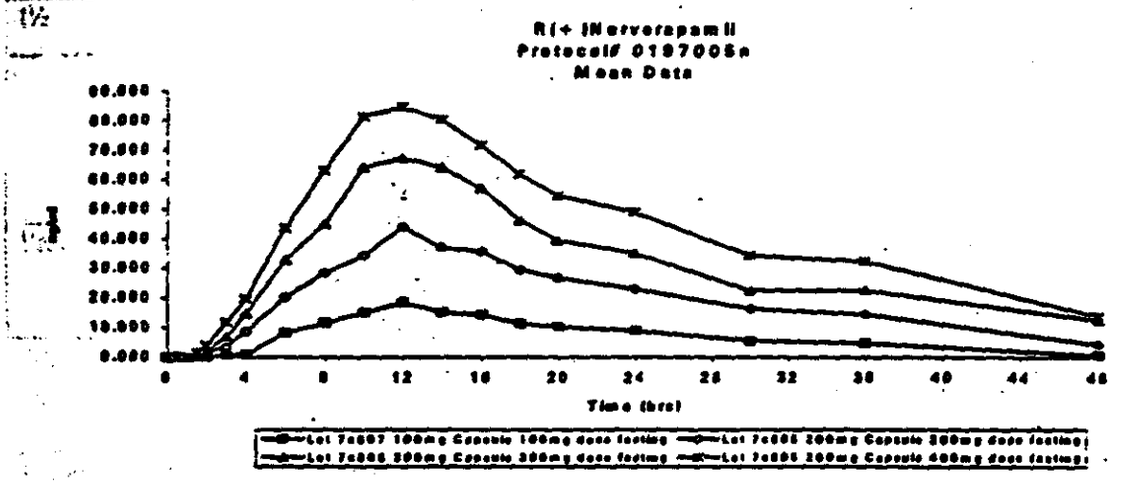


Figure 2b



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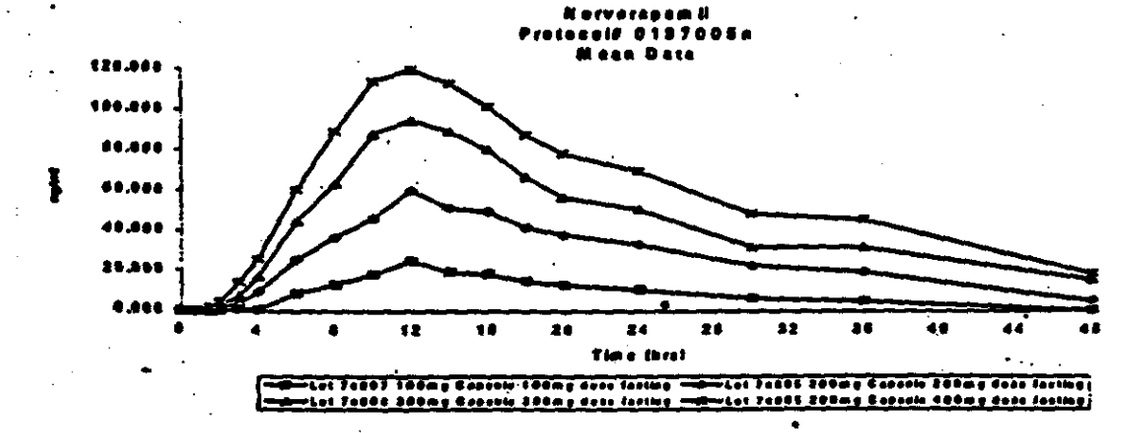

Appendix 5

A study in healthy volunteers to assess the effect of varying in-vitro dissolution rates on in-vivo performance of Elan's verapamil 240 mg formulation and Isoptin® 80 mg at single dose.

Study No. 1095006 Volume 1.33-34 Pages 1-686

Study initiated September 12th, 1996
Study completed October 15th, 1996

Investigators:

Objectives:

To compare the in-vivo pharmacokinetics of 4 Elan verapamil formulations with a range of in-vitro dissolution profiles to develop an in-vivo/in-vitro correlation in order to set dissolution specifications for Elan's verapamil.

Medication:

Treatment A: Verapamil 240 mg capsule (Elan, Veralan®) Lot # 6K 801 (slow dissolution) under fasting conditions.

Treatment B: Verapamil 240 mg capsule (Elan, Veralan®) Lot # 6K 802 (very slow dissolution) under fasting conditions.

Treatment C: Verapamil 240 mg capsule (Elan, Veralan®) Lot # 6K 803 (medium dissolution) under fasting conditions.

Treatment D: Verapamil 240 mg capsule (Elan, Veralan®) Lot number 6K 804 (fast dissolution) under fasting conditions.

Treatment E: Isoptin® 80 mg tablet (Knoll), lot number 614 (for deconvolution purposes).

Dose level:

A single oral dose of verapamil at 240 mg in each of 4 treatment periods and a single oral dose of verapamil 80 mg in a fifth treatment period.

Study population:

Ten healthy male volunteers, aged 18-40 (there will also be 3 stand-by volunteers). Two of the subjects were non-smokers.

Design:

The study was an open-label, single dose, five treatment, five period, five sequence randomized crossover design with a 6-day washout between treatment periods.

Each dose was administered with 240 ml of tap water and a mouth check was performed to ensure compliance. Subjects were dosed while standing and were requested to remain sitting or ambulatory for two hours after dosing and supine for a further 8 hours. Subjects were requested to fast for 10 hours prior to dosing and for 4 hours after dosing. Dosing will be between 8-10 am.

Adverse events were recorded.

Plasma levels of verapamil, norverapamil and their enantiomers were measured by blood sampling (7 ml) at:

0 hours (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30 and 36 hours after dosing with Veralan®.

0 hours (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 10 and 24 hours after dosing with Isoptin® 80 mg.

Samples were collected in EDTA vacutainers and plasma was isolated and frozen at -80 °C.

Assay procedures:

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Data analysis:

Pharmacokinetic parameters were calculated and analyzed as described previously.

AUC, Cmax, tmax and t ½ among treatment groups will be compared by ANOVA analysis and include subject, treatment, period, sequence and subject within sequence effects. The analysis will be carried out on both log-transformed and non-transformed data. Plasma concentrations for the Elan formulations will be deconvoluted using the PK parameters derived from Isoptin 80 mg.

The data obtained for norverapamil was not used in developing a correlation.

Additionally, due to the extended apparent elimination rate observed for the extended release batches, the AUC(0-36) was considered to be a more accurate estimate of verapamil exposure rather than AUC(inf).

Results:

1. Deconvolution-based IVIVC

Figure 2 shows the mean plasma-concentration-time curves for verapamil and figure 3 shows the mean in vivo release profiles. Table 4 shows the mean percentage of drug absorbed for each of the 4 batches at all the dissolution time points and figure 4 shows the regression for level A correlation for all batches.

Table 5 shows the geometric means of the observed and predicted AUC and Cmax data as well as the prediction error for verapamil. It is stated that on dose adjusting the AUC data from the IR product, the AUC was lower than that for the ER product for a majority of subjects. Therefore this underestimation in the impulse response resulted in an underestimation in the predicted PK parameters of the ER products, outside of the allowable range for a predictive correlation. This is why a convolution-based approach in which the IR results are not used for estimating the impulse response was used for the development of the IVIVC.

2. Convolution-based IVIVC

The plasma concentration time courses for all but the very slow batch (6K802) are predicted by this model. It is stated that as dissolution tended to be slower than absorption, if a time scaling factor had been incorporated into the IVIVC, then an IVIVC for all 4 formulations could be achieved.

Tables 7 and 8 show the observed and predicted Cmax and AUC data for each subject as well as the prediction error. All prediction errors for individual formulations are less than 15% and the overall mean absolute prediction error is less than 10%. Therefore, the sponsor concludes that since the individual prediction errors for AUC and Cmax are within an acceptable range, a predictable IVIVC is established.

Table 9 shows the dissolution specifications based on a $\leq$ 20% difference between the low versus the high predicted AUC and Cmax at the extremes of specifications.

Table 10 shows the predicted Cmax and AUC for all subjects at the extremes of the dissolution range. The ratio of the mean predicted AUC and Cmax of the low extreme over the high extreme was calculated and found to be 96.5% for Cmax and 80% for the AUC.

The reviewer used the convolution results provided by the sponsor to calculated average AUC profiles. The Cmax and AUC values for the average predicted profiles were calculated. The values were calculated under 2 conditions: 1) excluding the "very slow" batch (3-batch analysis) and 2) including the "very slow" batch (4-batch analysis). The results of this comparison yielded prediction errors which were above those stipulated in the FDA guidance document (15%). Therefore, even though the average prediction errors were below 10%, those for lot 804 (Table 1) were above 15%.

The dissolution data were fitted to an Emax model to get the dissolution parameters that were used in the convolution of the absorption rate with the disposition function to obtain the predicted plasma concentration time profiles. A regression analysis of the percent absorbed versus the percent dissolved for all 4 batches of verapamil PM was conducted, as well for the 3 batches, excluding the "very slow batch" (lot 802). The regression analysis results were used to convert the dissolution data into absorption rate data. The regression analysis of the 3 batches yielded the following values: intercept=-9.96 and slope= 1.327.

Subsequently, using the PK parameters provided by the sponsor (a=1.02 and α=0.185), the input and elimination functions were convolved to obtain the predicted plasma profiles. The values for the predicted AUC and Cmax were compared to those observed in vivo with verapamil PM. These results are included in Table 1, under "deconvolution analysis". The prediction errors obtained with both the 3- and 4- batch analyses were not acceptable, since the values were above those stipulated by the FDA guidance document on IVIVC studies. Specifically, although the average prediction errors were under 10 (9.3 and 9.5 for Cmax and AUC, respectively), the prediction errors for the fast lot (804) were -21.43 and -16.46 for Cmax and AUC, respectively, in the 3-batch analysis. Similarly, the average prediction errors were 15.307 and 14.76 for Cmax and AUC, respectively, for the 4-batch analysis.

These calculations show clearly that the deconvolution-based IVIVC is unacceptable, whether all 4 batches are included or whether the "very slow" batch is excluded. This conclusion is based on the guidance document for IVIVC studies which states that the average prediction error should not exceed 10% and that for any particular lot should not exceed 15%. Using the deconvolution-based IVIVC, some individual prediction errors exceeded 20%, regardless of whether all 4 batches are used or whether the "very slow" batch is excluded.

Using the convolution-based IVIVC method and excluding the "very slow" batch (3-batch analysis), the average prediction errors were within the guidelines, however, for lot number 804, the prediction error for the average profile is 16.748% (Table 1). According to the published FDA guidance on IVIVC studies, this is not acceptable unless there is an accompanying external predictability validation. Such an external

predictability test for the convolution-based IVIVC has not been carried out by the sponsor.

Two additional data sets from other studies submitted to the NDA were used in order to test the external predicatbility of the IVIVC model developed by the reviewer: one set of data were from the dose-proportionality study (using the 200 mg dose of verapamil PM), and the other set of data were from the food effect study (single dose study of 200 mg verapamil PM in the fasted state).

The dissolution parameters for each formulation used in the convolution spreadsheet are summarized in the table below:

	6K801	6K802	6K803	6K804	7C805	6H802
Dmax	86.86	83.02	101.35	104.03	95.6	97.16
D50	10.00	13.29	7.9	6.68	7.385	8.192
Gamma	2.833	3.367	1.91	1.712	1.896	2.1

The estimated average PK parameters determined by the sponsor were used to determine the input function. These values were:

Lot 6K801:

	Observed	Predicted	Prediction Error (%)
Cmax	65.66	68.31	-4.035
AUC	1044.18	1150	-10.13
Tmax	10.55		

Lot 6K803:

	Observed	Predicted	Prediction Error (%)
Cmax	89.41	83.85	6.218
AUC	1343	1304	2.90
Tmax	9.15		

Lot 6K804:

	Observed	Predicted	Prediction Error (%)
Cmax	93.31	76.84	17.10
AUC	1372	1178	14.13
Tmax	7.85		

External predictability of Dose-proportionality study (Lot 7C805) excluding lot 6K802:

	Observed	Predicted	Prediction Error (%)
Cmax	52.23	75.17	-43.92
AUC	785.19	1122	-42.89
Tmax	13.15	8.6	

External predictability Single dose study (food effect, Lot 6K802) excluding lot 6K802:

	Observed	Predicted	Prediction Error (%)
Cmax	55.23	73.52	-33.11
AUC	923.13	1132	-22.62
Tmax	9.8	9.55	

Excluding the fast lot (Lot 6K 804):

The data from lot 6K804 was omitted for the following series of calculations, in order to determine the prediction errors in the absence of this lot. The purpose for this analysis was because looking at the concentration time profiles (figure 2), it appears that the fast dissolution lot may not be behaving as expected. Therefore, at the biopharm day (August 6, 1998), it was suggested that the analyses be conducted in the absence of lot 804. The following is a summary of the findings when data from the "fast dissolution" lot is excluded from the calculations. The regression analysis was conducted and the values for the slope and intercept obtained are: slope=1.32 and intercept= -1.67.

Internal predictability test without lot 6K604:

Lot	Cmax			AUC		
	Observed	Predicted	Prediciton Error	Observed	Predicted	Prediciton Error
801	68.31	83.59	-22.37	1150	1197	-4.10
802	61.32	74.02	-20.711	1067	1015	4.87
803	83.85	91.15	-8.70	1304	1385	-6.18

External predictability of Dose-proportionality study (Lot 7C805) excluding lot 6K804:

	Observed	Predicted	Prediction Error (%)
Cmax	52.23	75.17	-43.9
AUC	785.19	1122	-42.89
Tmax	13.15	8.6	

External predictability Single dose study (food effect, Lot 6K802) excluding lot 6K804:

	Observed	Predicted	Prediction Error (%)
Cmax	55.23	75.52	-36.73
AUC	923.13	1132	-22.62
Tmax	9.8	9.55	

Clearly, the prediction errors obtained were not acceptable. In the absence of an external predictability test by the sponsor, using the convolution-based method used in the establishment of the level A correlation, the IVIVC study provided by the sponsor is deemed not predictive and unacceptable for use in the acquisition of a waiver for future bioequivalence studies.

Conclusions:

The objective of the study was to investigate the in vivo pharmacokinetics of 4 formulations with a range of in vitro dissolution profiles in order to develop an IVIVC. The slowest and fastest batches differed by 48% at 8 hours and by 20% at 24 hours.

A level A IVIVC was developed using a convolution-based approach excluding the slowest batch tested.

The sponsor concluded that the level A correlation developed was predictable.

The reviewer disagrees with the sponsor's conclusions. A predictable IVIVC was not developed. The reviewer developed a deconvolution-based IVIVC model (using all 4 batches of verapamil PM, as well as only 3 batches, with the omission of the very slow batch). However, the results obtained were equivocal (Table 1). The prediction error for lot 804 (very fast) was over 15%. Therefore, an external predictability test was conducted by the reviewer, using additional data from 2 other studies submitted to the NDA. The results obtained showed that the predicted values for AUC and Cmax were significantly different from the observed values for the same parameters.

The sponsor should therefore submit additional details about the convolution-based IVIVC model and include an external predictability test using the model established for this correlation.

In conclusion, the convolution-based approach gave better results due to the fact that the sponsor predicted the individual plasma profile for each subject using the average dissolution for each formulation and the individual disposition parameters for each subject. This procedure will minimize the variability and would thus result in more favorable prediction error values. Additionally, although the values of the prediction errors obtained in the convolution-based IVIVC do not indicate a need for an external predictability test, such a test would have been useful in determining the predictability of the model established by the sponsor. The reviewer used the dissolution data provided by the sponsor to determine prediction errors in the absence of lot 802 (very slow dissolution) and lot 804 (fast dissolution). However, these analyses did not yield acceptable prediction errors.

It should also be noted that in developing an IVIVC, it is generally customary to use the same drug in the IVIVC as that for which approval is being sought, and not another drug or formulation. In this particular case, since Verelan is very similar to verapamil PM, there will be no impact on the acceptability of the IVIVC.

Dissolution testing

The dissolution studies are located in volume No. 12, pages 214-242.

The dissolution testing was performed using standard USP apparatus I (rotating baskets). Lot number 7C805 which was one of the pivotal 200 mg capsule lots was used in these analyses.

The following table summarizes the findings of the dissolution testing conducted with Verapamil PM:

	AVERAGE DISSOLUTION UNDER VARIOUS CONDITIONS[a]											
Time	1	2	3	4	5	6	7	8	9	10	11	12
1 hr	4	5	5	4	4	5	5	4	5	5	5	4
2 hrs	9	10	10	9	8	10	10	9	9	10	10	9
4 hrs	21	22	22	24	20	22	22	23	22	23	23	24
6 hrs	37	36	36	40	36	36	36	37	38	37	37	40
8 hrs	53	49	50	51	52	50	50	50	54	51	50	52
10 hrs	65	60	61	58	64	60	60	57	65	62	61	59
11 hrs	69	64	65	61	68	64	65	60	70	66	65	61
12 hrs	73	67	69	65	72	68	68	62	73	69	68	63
14 hrs	78	72	73	658	78	73	73	65	79	74	73	66
16 hrs	83	75	77	67	82	76	77	67	83	78	76	68
18 hrs	86	78	80	69	86	79	79	69	86	80	79	70
20 hrs	88	80	82	71	88	81	82	71	88	82	81	71
22 hrs	90	82	84	73	90	83	84	73	90	85	83	73
24 hrs	91	84	86	74	91	85	86	74	92	86	85	75

a
1 0.1 N HCl, 75 rpm
2 pH 3.0 H2O, 75 rpm (protocol medium)
3 pH 3.0 Deionized H2O, 75 rpm
4 Phosphate Buffer pH 6.8, 75 rpm
5 0.1 N HCl, 50 rpm
6 pH 3.0 H2O, 50 rpm
7 pH 3.0 Deionized H2O, 50 rpm

8	Phosphate Buffer pH 6.8, 50 rpm
9	0.1 N HCl, 100 rpm
10	pH 3.0 H2O, 100 rpm
11	pH 3.0 Dionized H2O, 100 rpm
12	Phosphate Buffer pH 6.8, 100 rpm

The data show that the solubility of verapmil PM is reduced when dissolved in phosphate buffer pH 6.8. It is stated that the fumaric acid in the formulation results in the lowering of the pH of the water to 3.0. In 0.1 N HCl, the dissolution of verapamil was over 91% and in water pH 3.0, the dissolution was over 84% at 24 hours.

In the first 8 hours, the dissolution in all media evaluated was equivalent. Differences in the dissolution profiles were apparent in the 10-24 hour time period which is accounted for by the pH-dependent solubility of verapamil. Agitation did not appear to have an impact on the dissolution of verapamil. *(The dissolution profiles have been provided for review)*

The sponsor has set the following dissolution specifications:

1 hour:	%
4 hours:	%
8 hours:	%
11 hours:	%
24 hours:	%

The reviewer carried out the following analyses in order to ensure the validity of the sponsor's dissolution specifications.

The dissolution profiles from the following lots used in the clinical pharmacology studies were averaged to obtain an average dissolution profile. The average dissolution profile was convolved to obtain the predicted PK parameters (AUC, Tmax and Cmax). Additionally, the upper and lower limit dissolution profiles (from the specifications set forth by the sponsor) were also convolved to obtain the upper and lower limit predicted PK parameters. The upper and lower limit predicted PK parameters were compared to the average predicted PK parameters. The values obtained were as follows:

	Upper limit	Lower limit
Cmax	9.0%	3.5%

AUC	10.48%	12.09%

The following dissolution profiles were used:

Time	Lot 6K803	Lot 6H802	Lot 7C805	Average
1	6	5	5	5
4	21	17	22	20
8	50	46	51	49
11	68	65	66	66
24	90	88	86	88

The above average dissolution profile along with the upper and lower limit dissolution profiles were fitted to an Emax model to obtain the following absorption rates and predicted PK parameters:

	Lower	Average	Upper
Dmax	85.1	98.27	110
D50	9.78	7.87	6.88
Gamma	3.06	1.964	1.56
Cmax	71.19	73.82	80.55
AUC	964.35	1097	1212
Tmax	12.05	9.52	7.7

Conclusion:

The dissolution specifications proposed by the sponsor are acceptable to the division of Pharmaceutical Evaluation I

Table 2 Mean dissolution data

Time (h)	Lot 6K801 Slow	Lot 6K802 Very slow	Lot 6K803 Medium	Lot 6K804 Fast	Difference in extremes
1	2	1	6	7	6
4	7	3	21	29	26
8	29	12	50	60	48
11	50	29	68	74	43
24	80	73	90	93	20

Figure 2

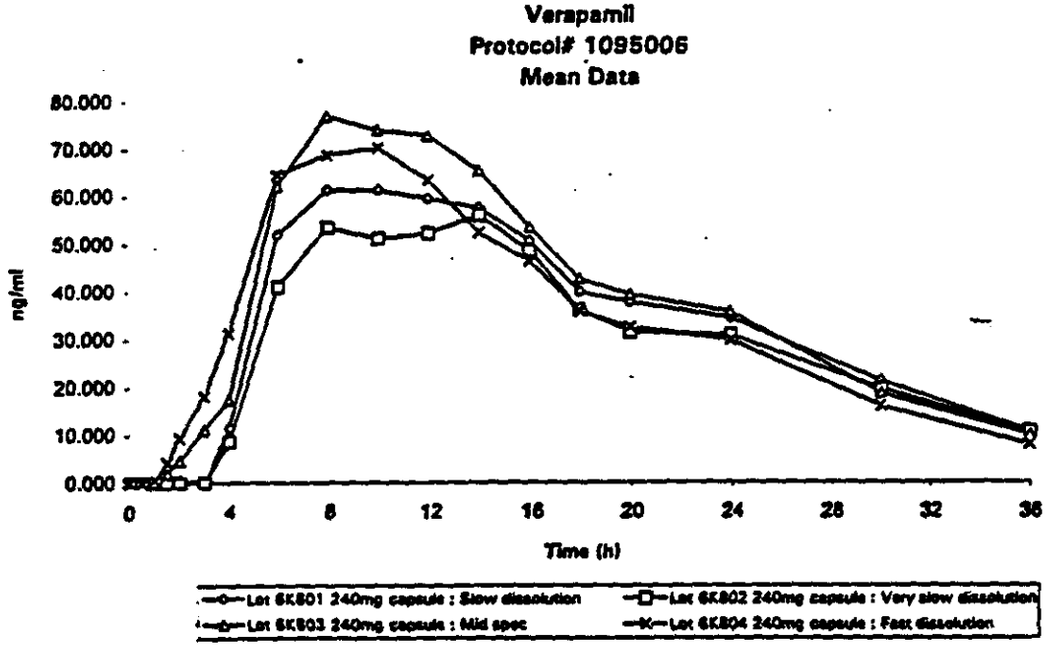

Figure 3

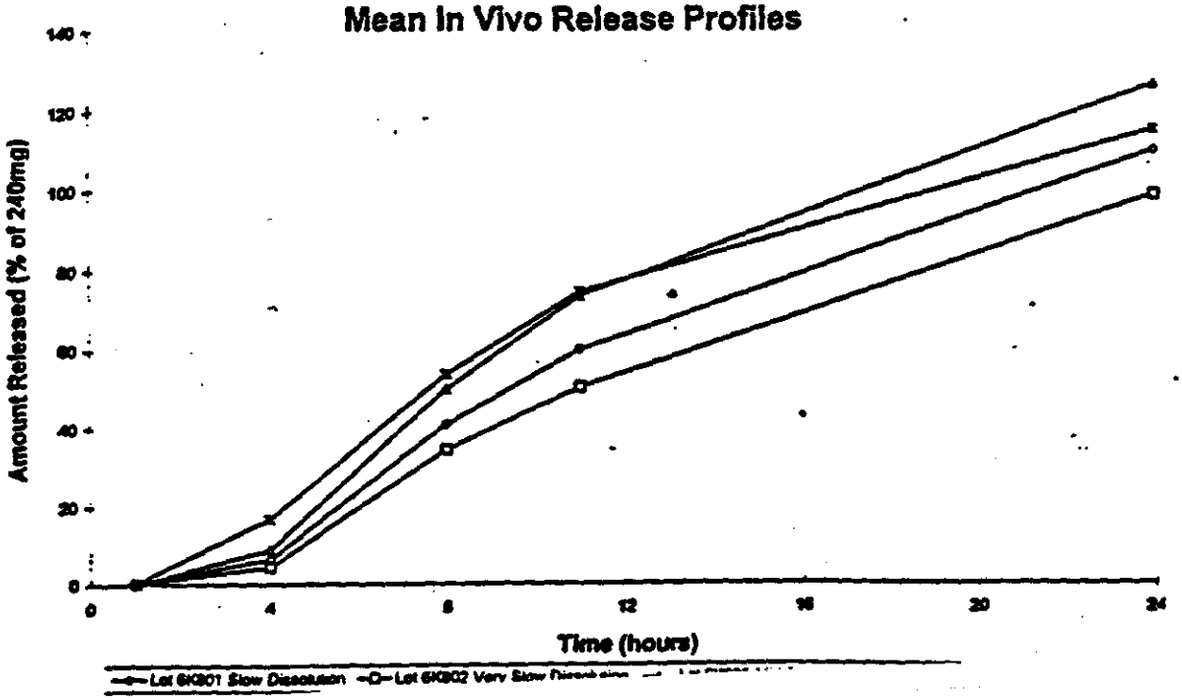

Table 4 Mean % absorbed

Time (h)	Lot 6K801	Lot 6K802	Lot 6K803	Lot 6K804
1	0.00	0.00	0.00	0.43
4	6.30	4.29	8.64	16.48
8	40.85	34.36	49.84	53.53
11	59.63	50.17	73.35	74.35
24	109.66	98.58	126.37	114.92
Regression	y=1.38*diss-2.96	y=1.31*diss+6.45	y=1.48*diss-18	y=1.30*diss-16.5
All batches	y= 1.26*diss - 3.34			

Figure 4

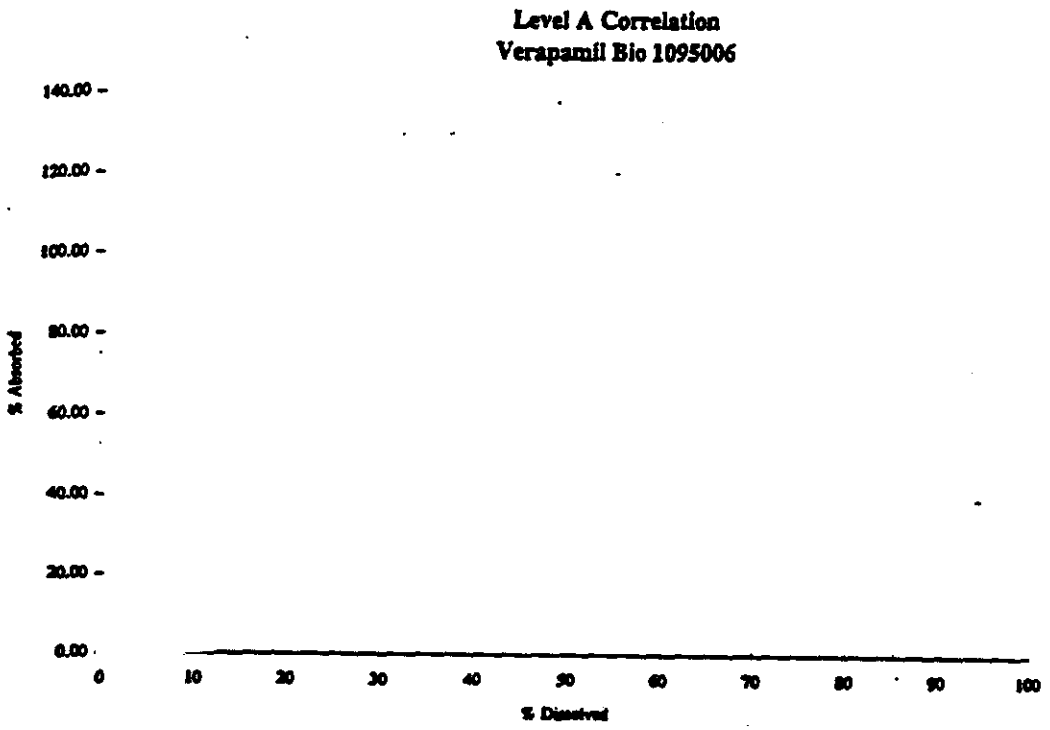

Table 5 Observed and Predicted Cmax and AUC

	Cmax			AUC		
	observed	predicted	prediction error (%)	observed	predicted	prediction error (%)
6K801	68.31	62.71	8.20	1150.00	950	17.39
6K802	61.32	44.17	27.97	1067.03	857	19.68
6K803	83.85	66.13	21.14	1304.42	1081	17.13
6K804	76.84	73.82	3.93	1178.44	1121	4.87

Table 7. Cmax(ng/ml) Predictability

	Lot 6K801		Lot 6K803		Lot 6K804	
Subject	Observed	Predicted	Observed	Predicted	Observed	Predicted
01						
02						
03						
04						
05						
06						
07						
08						
10						
209						
Geometric mean	68.31	63.08	83.85	73.46	76.84	75.98
Prediction error (%)	7.65		12.39		1.13	
Mean absolute prediction error (%)	7.06					

Table 8. AUC (0-36) (ng/ml.h) Predictability

	Lot 6K801		Lot 6K803		Lot 6K804	
Subject	Observed	Predicted	Observed	Predicted	Observed	Predicted
01						
02						
03						
04						
05						
06						
07						
08						
10						
209						
Geometric mean	1150.00	1036.98	1304.42	1218.53	1178.44	1219.35
Prediction error (%)	9.83		6.58		-3.47	
Mean absolute prediction error (%)	6.63					

Table 9. Proposed release specifications for Verapamil PM

	Specifications
Time (h)	%
1	
4	
8	
11	
24	NLT

Table 10. Predicted Cmax and AUC at extremes of dissolution specifications

Subject	Cmax		AUC	
	Low proposed	High proposed	Low proposed	High proposed
01				
02				
03				
04				
05				
06				
07				
08				
10				
209				
Geometric mean	65.70	68.08	1071.68	1339.70
low/high (%)				

Table 1

Convolution results

		3-batch analysis			4-batch analysis		
		Observed	Predicted	prediction error (%)	Observed	Predicted	prediction error (%)
Lot 801							
slow	Cmax	61.5	59	4.065041	61.5	65.4	-6.34146
	AUC	1030.5	1051	-1.98933	1030.5	1087.4	-5.52159
Lot 802							
very slow	Cmax				55.98	46.65	16.66667
	AUC				895.69	980.25	-9.44077
Lot 803							
medium	Cmax	76.9	75.7	1.560468	76.9	76.6	0.390117
	AUC	1194.8	1282.3	-7.3234	1194.8	1274.6	-6.67894
Lot 804							
fast	Cmax	70.2	77.9	-10.9687	70.21	79.5	-13.2317
	AUC	1101	1285.4	-16.7484	1101	1277.6	-16.04
Average	Cmax	69.5	70.9	5.53	67.7	67.6	9.156
	AUC	1108.8	1206.2	8.68	1063.8	1177.5	9.41

Deconvolution results

		3-batch analysis			4-batch analysis		
Lot 801		Observed	Predicted	prediction error (%)	Observed	Predicted	prediction error (%)
slow	Cmax	68.31	65.66	3.879373	68.31	62.71	8.197921
	AUC	1150	1045	9.130435	1150	950	17.3913
Lot 802							
very slow	Cmax				61.32	44.17	27.96804
	AUC				1067.03	857	19.68361
Lot 803							
medium	Cmax	83.85	89.41	-6.63089	83.85	66.13	21.13298
	AUC	1304	1343	-2.9908	1304	1081	17.10123
Lot 804							
fast	Cmax	76.84	93.31	-21.4341	76.84	73.82	3.930245
	AUC	1178	1372	-16.4686	1178.44	1121	4.874241
Average	Cmax	76.08	82.79	9.353	72.58	61.7	15.307
	AUC	1210.66	1253.3	9.52	1174.86	1002.25	14.76

Cmax units: ng/ml
AUC units: ng*h/ml

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Addendum to Biopharamceutics/Pharmacokinetics Review

NDA: 20-943

Sponsor: Elan Pharmaceutical Research, Gainesville, GA.

Drug: Verapmil PM (Circelan)

Formulation and Strengths: Extended release 100, 200 and 300 mg capsules.

Drug class: Calcium channel blocker

Type of review: Addendum to original review dated August 12th, 1998.

There is a typographical error in the original biopharmaceutics and pharmacokinetics review for Verpamil PM (NDA 20-943). This typographic error is in relation to the dissolution specifications and is located on pages 3, 11-12 and 66-67 of the original review. The dissoultion specifications are correctly listed in table 9 on page 71 of the review. The erroneous specifications described in the above-listed pages should be replaced with the following dissolution specifications proposed by the sponsor and accepted by the office of Clinical Pharmacology and Biopharmaceutics:

1 hour %
4 %
8 %
11 %
24 %

In addition, due to the above mentioned typographical error, other calculation errors ensued, and these are rectified in the following paragraphs. The following rectification is made to page 67 of the original review.

The upper and lower dissolution profiles based on the proposed specifications were convolved to obtain the predicted Cmax, AUC and Tmax corresponding to lots that are in the "upper" and "lower" limits of the dissolution specifications:

	Lower	**Average**	**Upper**
Dmax	82.52	98.27	110
D50	9.59	7.87	5.98
Gamma	3.64	1.96	1.15
Cmax	77.27	74.18	78.70
AUC	976	1103	1169
Tmax	12.02	9.25	5.9

When the upper and lower PK parameters are compared to the average PK parameters, the following values are obtained for the difference (this rectifies error on the bottom of page 66 and top of page 67):

	Lower vs Average	**Upper vs Agerage**
Cmax	3.98%	5.7%
AUC	11.52%	5.64%

The values obtained are within the acceptance limits set forth in the FDA guidance.

/S/

Nakissa Sadrieh, Ph.D.

Date: 8/21/98

/S/ 8/21/1998

RD/FT Patrick Marroum, Ph.D. Date:

CC List: NDA 20-943 , HFD-110 (Roeder); HFD-860 (Sadrieh, Marroum).