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PHARMACOKINETIC AND IN-VITRO CHARACTERISTICS OF SUSTAINED RELEASE VERAPAMIL PRODUCTS

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ABSTRACT

The in-vitro dissolution and in-vivo pharmacokinetics of two marketed sustained release formulations, Verelan *(V)* and Isoptin SR *(ISR)*, were compared. The effect of food on *V* was also examined in a separate study with conventional Isoptin *(I)* as a reference. Both sustained release preparations had extended dissolution profiles with 50% release times (T50%) of 4 hours for *ISR* and 8 hours for *V*. The extended in-vitro profile of *V* versus *ISR* was confirmed in-vivo with a Tmax of 7.3 hours compared to 5.0 hours, a Cmax of 114.3 compared to 171.0 and a peak to trough ratio of 3.8 compared to 10.1 for *V* and *ISR* respectively. In a second pharmacokinetic study the rate and extent of absorption of verapamil from *V* was shown to be unaffected by food.

INTRODUCTION

Verapamil is a slow channel-blocking agent which has anti-anginal, anti-hypertensive and anti-arrhythmic properties (1). This compound undergoes extensive 'first-pass' metabolism and its major metabolite is the N-demethylated metabolite nor-verapamil, which is pharmacologically active and can accumulate to levels equal to or greater than those of verapamil itself (2). Because of its relatively short elimination half-life, verapamil is normally prescribed in divided daily doses every 6 to 8 hours (3, 4). For this reason a number of sustained release formulations of verapamil have been developed to minimise dosage frequency.

One such sustained release formulation of verapamil (Verelan) has been shown to be effective in the treatment of hypertension (5) and angina (6, 7) when administered once daily. This formulation has been shown to have comparable bioavailability to divided doses of conventional verapamil under both single-dose and steady state conditions (8).

However, the effect of food on the absorption profile of this formulation has not been established nor has the formulation been compared to other sustained release verapamil formulations. For this reason a comparison of the in-vitro dissolution rates and the in-vivo absorption profiles of this new formulation and a widely available form, Isoptin SR was carried out. In addition, the rate and extent of absorption of verapamil following a single dose of

Verelan was evaluated under both fasted and fed conditions. For comparative purposes a conventional immediate release verapamil product, Isoptin, administered in divided doses, was administered under fasting conditions.

METHODS

Preparations:

(1) Isoptin (Knoll) Lot No. 20800535 *(I)*
(2) Isoptin SR (Knoll) Lot No. 21300528 *(ISR)*
(3) Verelan (Elan Pharma) Lot No. 5022 *(V)*

In Vitro Dissolution Studies

The dissolution rates of the formulations were determined using the B.P. rotating basket method at 75 rpm and a medium buffered at pH 3.0. Drug content was determined by ultraviolet absorption at 278 nm.

Clinical Study 1

Single Dose Comparison Of Two Sustained Release Formulations (*ISR* Versus *V*)

Six male volunteers between the ages of 21 and 35 and weighing 52.5 Kg and 82 Kg participated in this unblinded, randomised, two period, single dose, comparative study. All subjects gave informed consent and the study was approved by an independent ethical committee. *ISR* and *V* were administered as single 240 mg doses at 0 hr. Venous blood specimens

(10 ml) were obtained from each subject at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30 and 36 hours post dose. There was a minimum of seven days between study legs.

Clinical Study 2

Fasted Fed Study

Twelve male volunteers between the ages of 18 and 40 years and weighing 55.5 to 87.5 Kg participated in this unblinded, randomised, balanced, 3-period crossover study. All subjects gave informed consent and the study was approved by an independent ethical committee. Each study period lasted 48 hours and there were 7 days separating each drug administration sequence. All subjects fasted for 8 hours before dosing after which the diet of each volunteer depended on the treatment period to which they were assigned. Under 'fasted conditions' volunteers were fasted for 4 hours after drug administration. Under 'fed conditions' volunteers received *V* 10 minutes after finishing a standard breakfast of double bacon, double egg, toast and a glass of milk. All subjects received lunch after the 4 hour sampling time and a light snack after the 18 hour sampling time.

Venous blood specimens (7 ml) were obtained from each subject at 0, 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 14, 16, 17, 18, 19, 20, 22, 24, 26, 28, 36 and 48 hours following administration of both *I* and *V*.

Plasma Concentrations of Verapamil and Nor-Verapamil

Heparinized blood specimens were centrifuged at 3000 rpm (800 g) for 15 minutes and the plasma separated and stored at -203C until required for assay. Concentrations of verapamil and nor-verapamil in plasma were determined by high performance liquid chromatography on a normal phase column using fluorescence detection at an excitation wavelength of 220 nm and an emission wavelength of 313 nm. The limit of detection of the assay was 2 ng/ml for both verapamil and nor-verapamil.

Statistical Analysis

Where mean results are given the values are shown together with values of standard error of the mean ($\pm$ s.e.m).

Comparisons were made using analysis of variance procedures (ANOVA) appropriate to the final balance of each study. Results were judged to be significant based upon the 95% probability values ($p \leq 0.05$).

RESULTS

Dissolution Data

Figure 1 shows the mean in vitro dissolution profiles for both *ISR* and *V*. *ISR* achieved 50% release at about 4 hours and 90% release at about 8 hours. *V* had a more extended profile

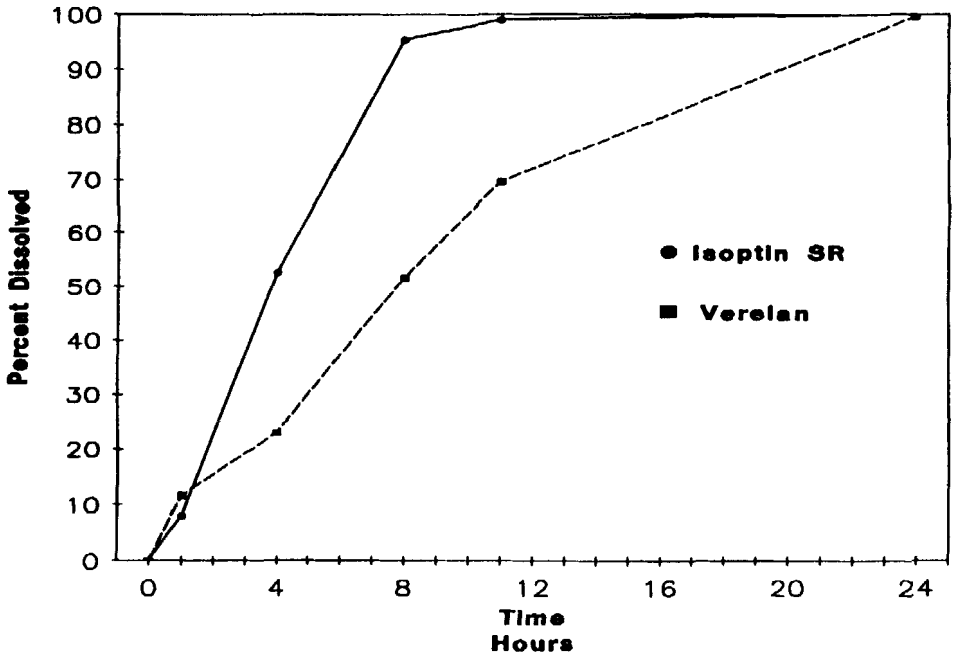

Figure 1
In-Vitro Dissolution Profiles

with 50% release at 8 hours, 70% release at 11 hours and 100% release at 24 hours.

Single Dose Comparative Study (Clinical Study 1)

Figures 2 and 3 show the mean verapamil and nor-verapamil plasma profiles following single 240 mg doses of *ISR* and *V*. Tables 1 and 2 summarise selected pharmacokinetic parameters from this comparison for both verapamil and nor-verapamil. In terms of extent of absorption *V* and *ISR* were bioequivalent with a mean relative bioavailability, *V/ISR*, of 112%. Mean peak verapamil and nor-verapamil concentrations

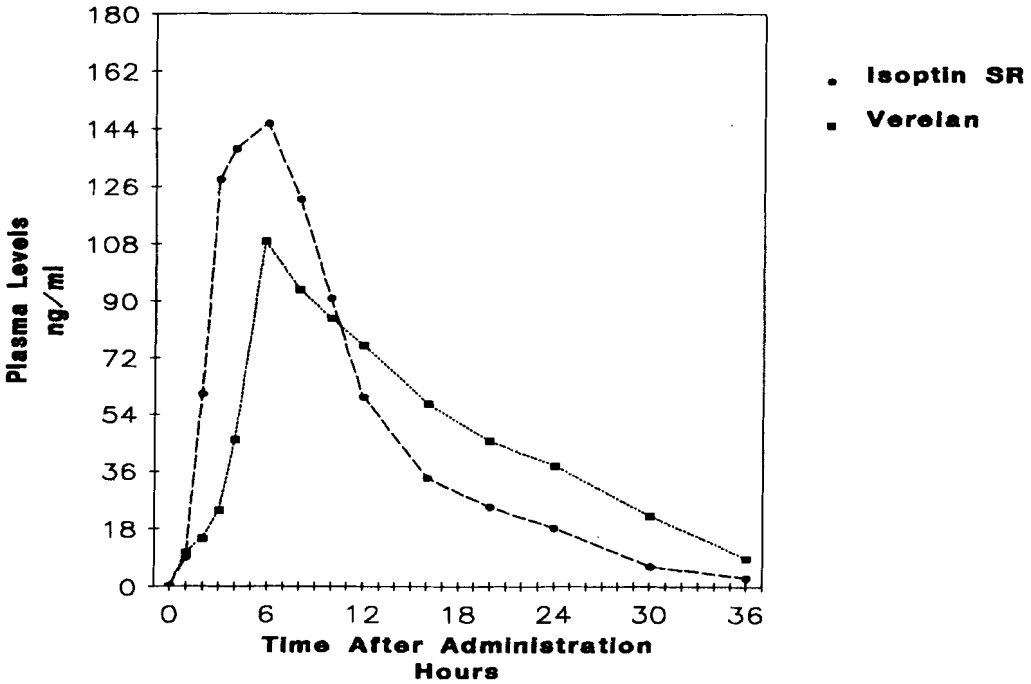

Figure 2

Plasma Verapamil Levels

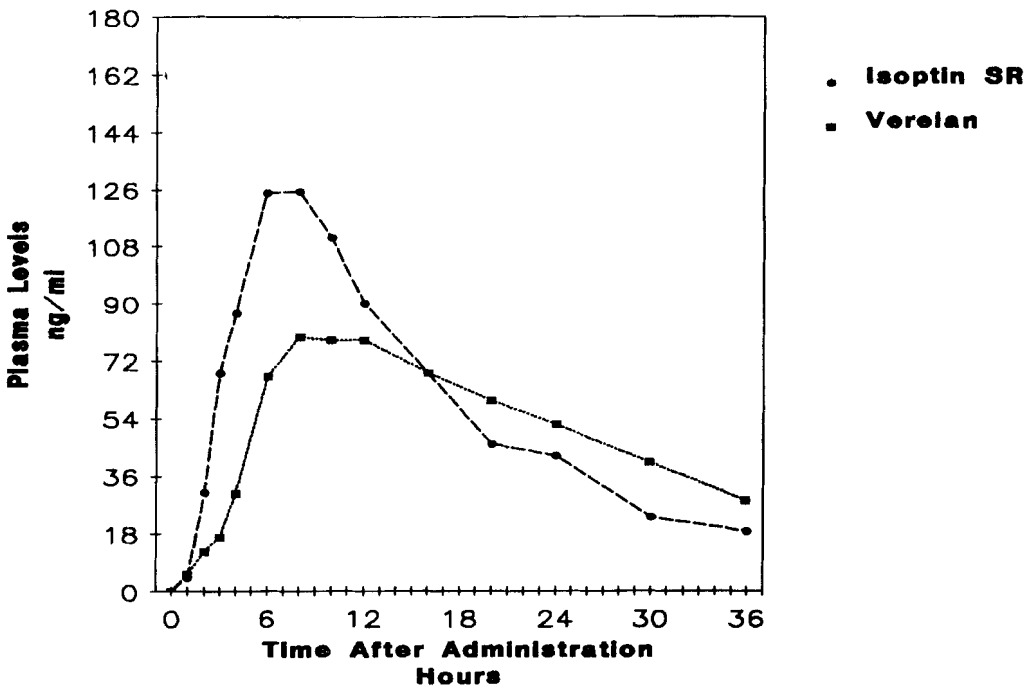

Figure 3

Plasma Nor-Verapamil Levels

Table 1

Summary of Plasma Verapamil Pharmacokinetic Parameters Following 240mg Single Dose Administration of Two Verapamil Sustained Release Formulations.

Parameter	Isoptin SR	Verelan
AUC(finite)	1670.92+/-909.32	1675.00+/-518.09
AUC(infinite)	1743.28+/-934.92	1795.06+/-565.50
F(infinite)		112.04+/-28.30
Tmax	5.00+/-2.00	7.33+/-1.63*
Cmax	170.98+/-78.20	114.30+/-33.86*
Kel	0.116+/-0.021	0.079+/-0.016**
T1/2	6.15+/-1.42	9.16+/-2.08**
Cmax/C(t)	10.14+/-4.05	3.76+/-2.78**

Table 2

Summary of Plasma Nor-Verapamil Pharmacokinetic Parameters Following a 240mg Single Dose Administration of Two Verapamil Formulations.

Parameter	Isoptin SR	Verelan
AUC(finite)	2088.40+/-974.22	1862.72+/-454.05
AUC(infinite)	2378.42+/-1149.68	2288.71+/-665.41
F(infinite)		106.00
Tmax	6.83+/-2.40	9.67+/-1.97
Cmax	130.82+/-55.20	87.30+/-18.08*
Kel	0.068+/-0.008	0.056+/-0.017
T1/2	10.38+/-1.29	13.56+/-4.25
Cmax/C(t)	3.52+/-0.88	1.79+/-0.60**

*p<=0.05 compared to Isoptin SR

**p<=0.01 compared to Isoptin SR

(Cmax) after *V* were significantly lower than after *ISR* (verapamil; 114.3 and 171.0 respectively: norverapamil; 87.3 and 130.8 respectively). The speed of absorption measured as time to peak concentration of verapamil (Tmax), was significantly slower ($p < 0.05$) after *V*, (7.3 hours) compared to the reference (5.0 hours). Extension of the plasma concentration time profile for *V* was demonstrated by a significantly lower ($p < 0.01$) peak-to-24 hour trough ratio for *V* (3.8) compared to *ISR* (10.1). Intersubject variability [measured as the percentage coefficients of variation (% CV) of AUC and Cmax values] was higher for *ISR* than for *V* with respective mean values of 54.4% and 45.7% for *ISR* and 30.9% and 29.6% for *V*.

Fasted/Fed Study (Clinical Study 2)

Figures 4 and 5 show the mean verapamil and nor-verapamil concentrations following administration of *I* at doses of 80 mg at 0, 8 and 16 hours and *V* as a single 240 mg dose at 0 hour under both fasted and fed conditions.

Tables 3 and 4 summarise mean pharmacokinetic characteristics of these formulations based on both verapamil and nor-verapamil concentrations.

Food had no significant effect on the bioavailability of *V*, based upon measurements of both verapamil and nor-verapamil concentrations. Values of areas under the concentration/time curve of

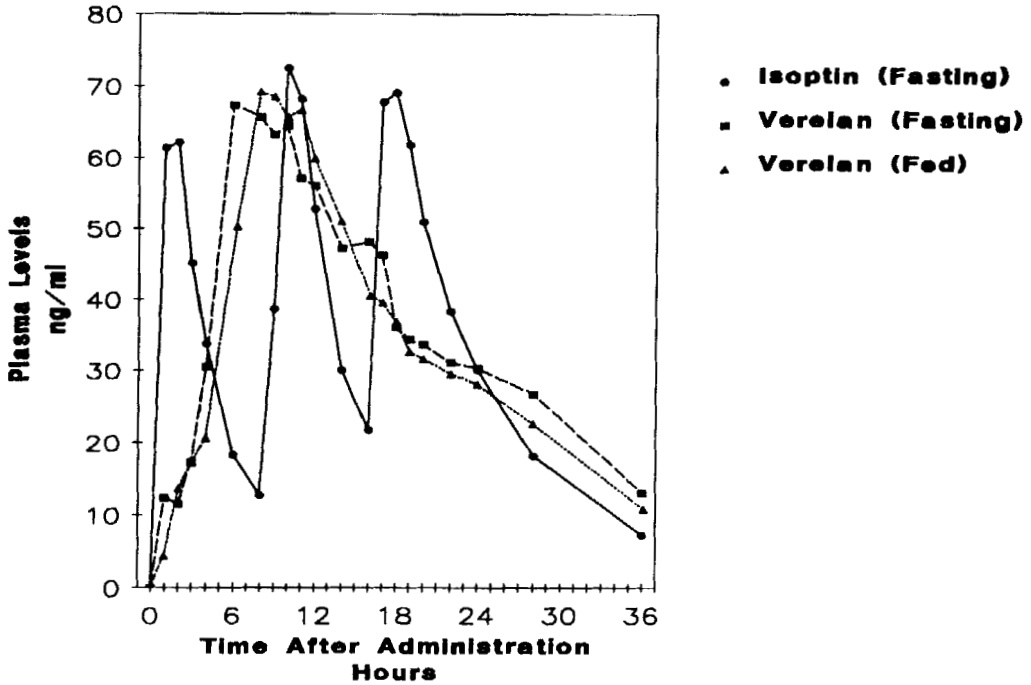

Figure 4

Plasma Verapamil Levels

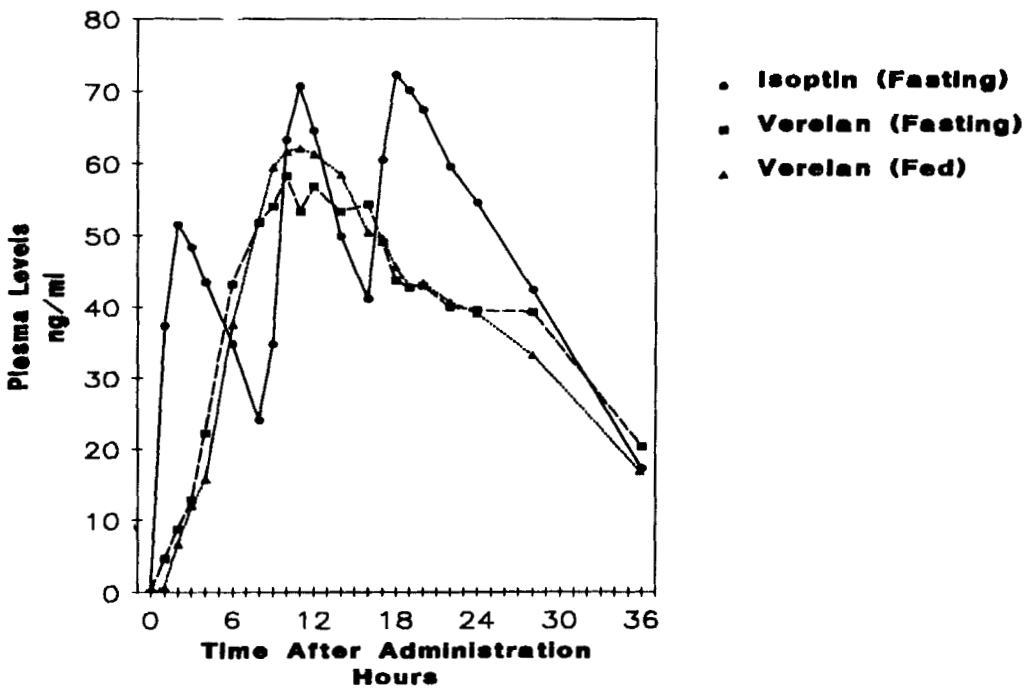

Figure 5

Plasma Nor-Verapamil Levels

Table 3

Summary of Verapamil Pharmcokinetic Parameters, Effect of Food Study.

Parameter	Isoptin(fasting)	Verelan(fasting)	Verelan(fed)
AUC(0-48hr)	1270.96+/-549.22	1411.34+/-599.96	1297.07+/-535.15
Ft(%)	100.00	120.11+/-40.39	105.33+/-32.87
Tmax	1.75+/-0.87	9.75+/-3.38**	9.00+/-1.13**
Cmax	94.96+/-42.31	76.56+/-30.38	76.77+/-30.55
Cmax/C24hr	3.22+/-1.16	2.59+/-0.71	2.77+/-0.55
Kel	0.091+/-0.037	0.058+/-0.017**	0.065+/-0.016**
T1/2	9.66+/-7.04	13.10+/-4.16	11.31+/-2.86

Table 4

Summary of Nor-Verapamil Pharmacokinetic Parameters, Effect of Food Study.

Parameter	Isoptin(fasting)	Verelan(fasting)	Verelan(fed)
AUC(0-48hr)	1786.99+/-456.31	1552.39+/-479.76*	1484.13+/-361.01**
Ft(%)	100.00	88.31+/-31.13	84.54+/-20.97
Tmax	3.00+/-1.76	11.17+/-2.41**	11.83+/-2.55**
Cmax	76.69+/-18.51	63.42+/-16.48**	69.02+/-14.28*
Cmax/C24hr	1.51+/-0.42	1.72+/-0.43	1.87+/-0.55*
Kel	0.091+/-0.026	0.059+/-0.016**	0.068+/-0.023**
T1/2	8.18+/-2.35	12.53+/-3.08**	11.50+/-4.56**

*p<=0.05 compared with Isoptin

**p<=0.01 compared with Isoptin

verapamil were slightly higher after *V* (fasted and fed) than after *I*. Values of areas under the concentration/time curve of nor-verapamil were slightly lower for *V*.

Food had no effect on the time to peak plasma verapamil and nor-verapamil concentrations following administration of *V*.

V demonstrated a significantly delayed ($p < 0.01$) time to peak plasma verapamil concentration (9.75 h and 9.0 h under fasting and fed conditions respectively) compared with the reference product which peaked at 1.75 h. Similarly, the tmax value for *V* based on nor-verapamil data was significantly delayed relative to I under both fasting and fed conditions.

The maximum verapamil and nor-verapamil concentration (Cmax) was essentially the same under both fasting and fed conditions following *V* administration. *I* showed a slightly higher peak verapamil concentration relative to *V*, although this difference was not statistically significant. Based on nor-verapamil data, *I* demonstrated a significantly greater Cmax value compared with *V* under fasting ($p < 0.01$) and fed ($p < 0.05$) conditions.

Using the coefficient of variation (%CV) as an index of intersubject variation, *V* under both fasting and fed conditions demonstrated a lower level of intersubject variability in terms of AUC and Cmax

compared with *I*, suggesting more consistent absorption.

DISCUSSION

The single dose and steady state pharmacokinetic profile of *V* compared to immediate release verapamil has been documented previously (8). In the present studies this formulation was compared to another sustained release formulation in terms of both in-vitro dissolution rates and single-dose pharmacokinetic characteristics. The effect of food on the rate and extent of absorption from *V* was also evaluated.

The dissolution profile of *ISR* showed 50% release after 4 hours and 90% release after 8 hours. This compared with 50% release after 8 hours for the new formulation and 70% after 11 hours. The extended in-vitro profile was confirmed in-vivo where the faster in-vitro product had a significantly higher peak concentration (Cmax) combined with a significantly shorter time to maximum concentration (tmax). *V* also exhibited an extended plasma profile in terms of peak to trough ratio which was significantly lower than the reference.

Recently the effect of food on the pharmacokinetic profile of drug products, and on sustained release formulations in particular, has been of concern. Studies on several products have resulted in the inclusion of precautions in the dosage instructions. It is important, therefore, to

establish what these effects are likely to be for each formulation and if required amend the dosing instructions accordingly.

From the results of our study it appears that food has minimal effects on the absorption of *V*. The rate of absorption of verapamil, reflected in the tmax values, was very similar before and after food, with a difference of only 0.75 h between fasting and fed conditions. The same result was seen with nor-verapamil.

Similarly, little effect on the extent of verapamil and nor-verapamil absorption was observed following *V* administration under fasting and fed conditions. While verapamil and nor-verapamil AUC values were slightly lower under fed conditions, no significant difference was observed compared with fasting conditions, and in fact, under fed conditions, *V* was 90% bioavailable based on verapamil data and 95% bioavailable based on nor-verapamil data respectively, relative to fasting conditions. Also, while under fed conditions, *V* showed a slightly higher Cmax value for both verapamil and nor-verapamil data compared with fasting conditions, these differences were small and were not found to be statistically significant. In addition, the ratio of verapamil to nor-verapamil values were not significantly different under fasting and fed conditions reflecting the similar proportionate metabolism of verapamil to nor-verapamil under both conditions.

Food did not affect the apparent elimination characteristics of *V*.

In summary, therefore, we have confirmed that this new verapamil formulation exhibits in-vivo and in-vitro characteristics consistent with its suitability for once-daily dosing. The pharmacokinetic profile is not significantly influenced by food.

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