CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19787/S003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUL 2 1998

S-003

Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-787 N (IM) 633
Letter Date: April 15th, 1997
Drug: Amlodipine besylate (Norvasc)
Sponsor: Pfizer

Reviewer: Nakissa Sadrieh Ph.D.

Re: "The effect of grapefruit juice on the pharmacokinetics of amlodipine in normal volunteers". Protocol # 053-017.

Background:

Amlodipine is a calcium channel blocker of the family of 1,4 dihydropyridines.

Recent results of clinical pharmacology studies have shown that grapefruit juice markedly inhibits the metabolism of some dihydropyridine calcium channel blockers such as felodipine, nitrendipine and to some extent nifedipine resulting in an increase in bioavailability. The interaction with the dihydropyridine calcium channel blockers is described as a "class effect", as an oxidation of the dihydropyridine ring to the corresponding pyridine derivative which is a major metabolic route for all drugs in this class. Bailey et al., (Lancet 1991, 337:268-269) is reported to have shown that the effect of grapefruit juice may not be limited to CYP3A4, and that other CYP isozymes may be involved.

In this study, the single dose PK of amlodipine was characterized following IV administration with and without grapefruit juice. Grapefruit juice was administered with breakfast throughout the duration of the study.

Results:

Please refer to the attached tables and figures for the results of the study.

Briefly, AUC(0-inf) for either oral or IV amlodipine was not affected by whether grapefruit juice was or was not consumed (table 5.1.1). the mean ratio for absolute bioavailability after grapefruit juice compared with placebo was 108% with a 95% confidence interval.

Similarly, there was no significant change in Cmax after IV or oral dosing with grapefruit juice compared to placebo. The ratio of oral amlodipine with or without grapefruit juice was 107% with the 95% confidence limits between 91.7-125%.

The mean AUC(0-96) and AUC(0-24)for the R- and S- enantiomers and the S/R ratio did not show a statistically significant difference with or without grapefruit juice administration (table 5.3.1 and 5.3.2). Figures 5 and 6 show the mean plasma concentrations of R- and S- amlodipine over time after IV and oral administration, respectively.

The absolute Cmax values of the R- and S- enantiomers after IV dosing and grapefruit juice showed a decrease of 24% and 26% for Cmax, as compared to the Cmax values after placebo (table 5.3.1). No reason is provided by the sponsor for this observed effect. However, the mean plasma concentration at 8 hours (C8) for the R- and S-enantiomers after oral dosing showed no statistical difference between grapefruit juice and placebo (table 5.3.2)

There was no statistically significant change in supine or standing diastolic or systolic blood pressure and heart rate.

Only one subject was discontinued from the study after receiving amlodipine and grapefruit juice due to a tension headache.

It is concluded that the oral pharmacokinetics of a single dose of 10 mg amlodipine were not affected by grapefruit juice.

Comments: Under the "Drug Interactions" section of the package insert, the following statement should be added: "no significant drug interactions were noted in a study in 20 healthy male volunteers taking a single oral dose of 10 mg amlodipine with grapefruit juice."

Recommendations: The following statement should be added to the package insert:

> "No significant drug interactions were noted in a study in 20 healthy male volunteers taking a single oral dose of 10 mg amlodipine with grapefruit juice."

/S/ 7/2/98

Nakissa Sadrieh, Ph.D.

RD/FT initialed by Patrick Marroum, Ph.D. /S/ 7/2/98

cc: NDA19-787, HFD-110 (Roeder), HFD-860 (Sadrieh), CDER document room, Barbara Murphy.

Appendix 1

The effect of grapefruitjuice on the pharmacokinetics of amlodipine in normal volunteers.

Study No. 053-017 **Volume 1.1** **Pages 1-524**

Study initiated January 20th, 1994
Study completed March 31st, 1994

Investigators:

Objectives:

To examine the effect of grapefruit juice on the PK and PD of amlodipine after oral and intravenous administration.

Additionally, the effects of grapefruit juice on the disposition of the enantiomers of amlodipine following oral administration were also examined.

Medication and dose level:

Amlodipine oral tablets (FID#WW-89-018)
Amlodipine intravenous infusion (FID#WW-86-001)

Study population:

Twenty healthy male volunteers ages 20-45 who were within 10% of ideal body weight. Females were excluded from the study.

Design:

This was a placebo-controlled, open, randomized, crossover study using single doses of amlodipine 10 mg administered with and without grapefruit juice. Amlodipine was administered orally and intravenously.

Each subject was to receive a single dose of oral amlodipine on 2 study days and a single dose of intravenous amlodipine on 2 study days, with at least 14 days between the doses.

Subjects were administered single oral doses (1x10 mg) and single intravenous infusion doses (1x10mg) in an open fashion under fasting conditions (8 hours prior to and 4 hours after) in the morning. Oral drug was administered with 240 ml water or grapefruit juice. Intravenous dose was administered by infusion over 10 minutes, while a continuous EEG was monitored. Subjects consumed 240 ml of grapefruit juice or placebo just prior to commencement of the infusion. During the treatment sequences in which grapefruit juice was required, the subjects were to take grapefruit juice with breakfast on each of the 9 days of blood sampling for amlodipine concentrations.

Twenty four hours after dosing, the subjects were discharged from the research facility, but they were to return to the clinical facility at 36, 48, 72, 96, 120, 144, 168, 192 and 216 hours after each dose of amlodipine.

Blood samples for the determination of plasma amlodipine concentrations were collected prior to and up to 216 hours after each dose of the study drug. Blood samples were collected at the following time points: prior to dosing orally or at the end of the infusion period, 30 and 45 minutes after dosing, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours after amlodipine administration (*amlodipine half-life is 30-50 hours*). For the infusion studies, additonal samples were to be collected at 10 minutes prior to the start of infusion, 5 minutes into the infusion (at midpoint), at the end of the infusion, and 5 and 15 minutes after the end of the infusion.

Pharmacodynamic measurements included blood pressure and pulse rate measurements prior to dosing, at 5, 15, 30, 45 minutes, 1, 1.25, 1.5, 1.75, 2, 2.25, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours after dosing with amlodipine.

Assay procedures:

Data analysis:

PK parameters such as AUC (0-inf), Cmax, Tmax, Kel, and t ½, were determined. Natural log-transformed AUC, Cmax, and absolute bioavaillbility (F), as well as the untransformed Tmax, Kel, total Cl and steady state volume of distribution (Vdss) were analyzed using an ANOVA model. SAS was used for these analyses. A 5% level of significance was used to test the effects.

The study was designed to have at least 80% power at the 5% level of significance of detecting 20% difference in the AUC of amlodipine based on a previous Pfizer study where the mean SD for 12 subjects given single oral doses of amlodipine at 10 mg was 238±53 ng.hr/ml.

Results:

Please refer to the attached tables and figures for the results of the study.

Briefly, AUC(0-inf) for either oral or IV amlodipine was not affected by whether grapefruit juice was or was not consumed (table 5.1.1). the mean ratio for absolute bioavailability after grapefruit juice compared with placebo was 108% with a 95% confidence interval.

Similarly, there was no significant change in Cmax after IV or oral dosing with grapefruit juice compared to placebo. The ratio of oral amlodipine with or without grapefruit juice was 107% with the 95% confidence limits between 91.7-125%.

The mean AUC(0-96) and AUC(0-24)for the R- and S- enantiomers and the S/R ratio did not show a statistically significant difference with or without grapefruit juice administration (table 5.3.1 and 5.3.2). Figures 5 and 6 show the mean plasma concentrations of R- and S- amlodipine over time after IV and oral administration, respectively.

The absolute Cmax values of the R- and S- enantiomers after IV dosing and grapefruit juice showed a decrease of 24% and 26% for Cmax, as compared to the Cmax values after placebo (table 5.3.1). No reason is provided by the sponsor for this observed effect. However, the mean plasma concentration at 8 hours (C8) for the R- and S-enantiomers after oral dosing showed no statistical difference between grapefruit juice and placebo (table 5.3.2)

There was no statistically significant change in supine or standing diastolic or systolic blood pressure and heart rate.

Only one subject was discontinued from the study after receiving amlodipine and grapefruit juice due to a tension headache.

It is concluded that the oral pharmacokinetics of amlodipine were not affected by grapefruit juice.

Table 5.1.1. Summary of Pharmacokinetics of Amlodipine Following IV and Oral Doses to Subjects with Daily Consumption of Grapefruit Juice or Placebo

Subject Number	Cmax (ng/ml)	Tmax (hr)	k_{el} (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	Cl_t (ml/min/kg)	Vd_{ss} (L/kg)
TREATMENT A (IV administration to subjects consuming grapefruit juice)								
Mean	30.1	0.0	0.0161	43.1	349	374	6.65	22.7
S.D.	12.1		0.0029		84	88	1.99	5.1
CV(%)	40.1		18.0		24.0	23.5	29.9	22.4
TREATMENT B (IV administration to placebo subjects not consuming grapefruit juice)								
Mean	34.8	0.0	0.0181	38.3	343	358	6.93	21.0
S.D.	13.7	0.1	0.0041		83	88	1.72	3.8
CV(%)	39.3		23.0		24.2	24.6	24.9	17.9

Subject Number	Cmax (ng/ml)	Tmax (hr)	k_{el} (hr^{-1})	$T_{1/2}$ (hr)	AUC_{last} (ng•hr/ml)	$AUC_{0-\infty}$ (ng•hr/ml)	F
TREATMENT C (oral administration to placebo subjects not consuming grapefruit juice)							
Mean	5.8	7.9	0.0177	39.2	276	293	0.81
S.D.	1.1	1.7	0.0034	-	58	58	0.14
CV(%)	19	22	19	-	21	20	17
TREATMENT D (oral administration to subjects consuming grapefruit juice)							
Mean	6.2	7.6	0.0166	41.8	294	315	0.88*
S.D.	1.1	1.4	0.0038	-	73	76	0.15
CV(%)	19	18	23	-	25	24	17

* Relative to placebo IV dose.

TABLE 5.1.2
AMLODIPINE PROTOCOL 053-017
SUMMARY OF STATISTICAL ANALYSES OF AMLODIPINE PHARMACOKINETIC PARAMETERS
(AUC (0-inf), CMAX, F, TMAX, KEL, CLEARANCE AND VDSS)

Pharmacokinetic Parameter	Comparison	Adjusted Geometric Means	Ratio	95% Confidence Limits
AUC(0-inf) (ng.hr/ml)	IV + Juice vs IV + Placebo	367.3 vs 358.3	102.5%	(94.8%, 110.9%)
	Oral + Placebo vs IV + Placebo	292.4 vs 358.3	81.6%	(75.5%, 88.3%)
	Oral + Juice vs IV + Placebo	315.1 vs 358.3	88.0%	(81.6%, 94.8%)
	Oral + Juice vs Oral + Placebo	315.1 vs 292.4	107.8%	(99.7%, 116.5%)
Cmax (ng/ml)	IV + Juice vs IV + Placebo	29.9 vs 34.8	85.9%	(73.6%, 100.3%)
	Oral + Juice vs Oral + Placebo	6.2 vs 5.8	107.1%	(91.7%, 125.0%)
F (%)	Juice vs Placebo	87.9% vs 81.5%	107.9%	(98.4%, 118.4%)
		Adjusted Means	Difference	
Tmax (hr)	Oral + Juice vs Oral + Placebo	7.6 vs 7.8	-0.2	(-0.9, 0.5)
Kel (/hr)	IV + Juice vs IV + Placebo	0.0159 vs 0.0181	-0.0022	(-0.0039,-0.0005)
	Oral + Juice vs Oral + Placebo	0.0166 vs 0.0176	-0.0010	(-0.0026, 0.0007)
C. ance (ml/min/kg)	IV + Juice vs IV + Placebo	6.8 vs 6.9	-0.2	(-1.1, 0.8)
Vdss (L/kg)	IV + Juice vs IV + Placebo	22.9 vs 21.0	1.9	(-0.7, 4.5)

Source Data: Appendix IIIB, Tables 1-7 Date of Data Extraction: 06NOV96 Date of Table Generation: 10FEB97

Figure 5. Mean Plasma Concentrations of R- and S-Amlodipine Following 1-Minute Infusion of 10 mg to Subjects Consuming Either Grapefruit Juice or Placebo (water)

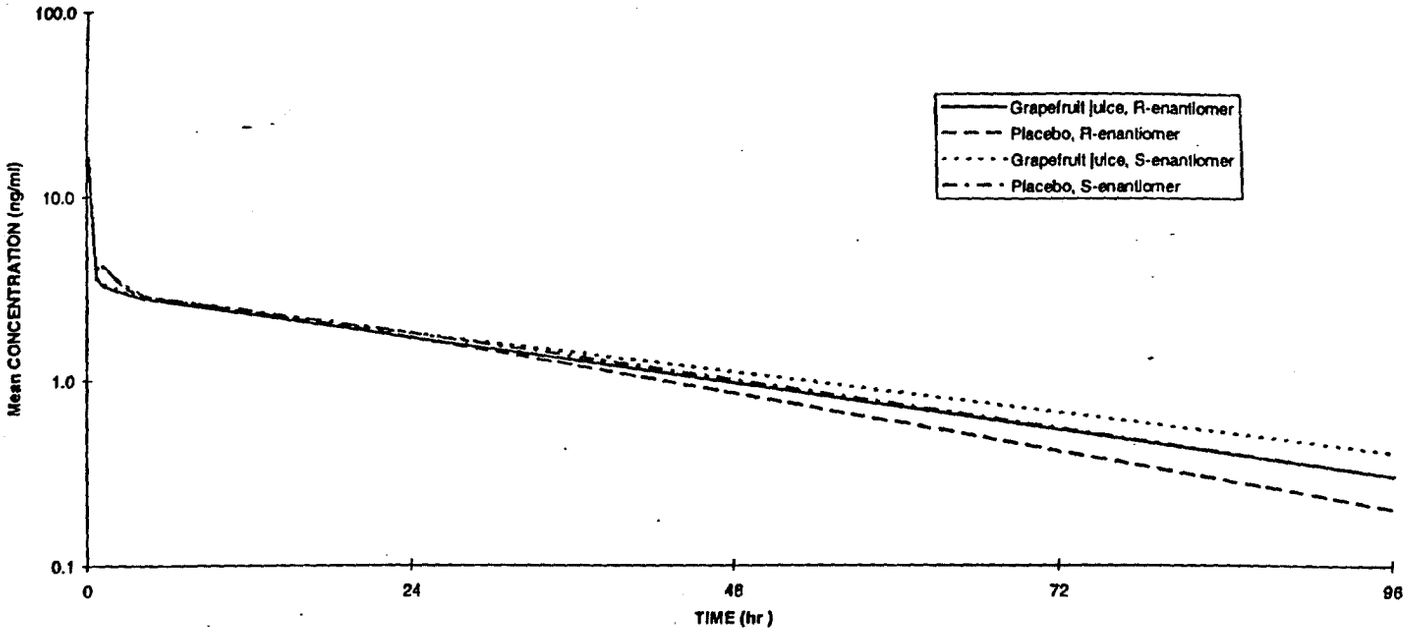

Figure 6. Mean Plasma Concentrations of R- and S-Amlodipine Following Oral Doses of 10 mg to Subjects Consuming Either Grapefruit Juice or Placebo (water)

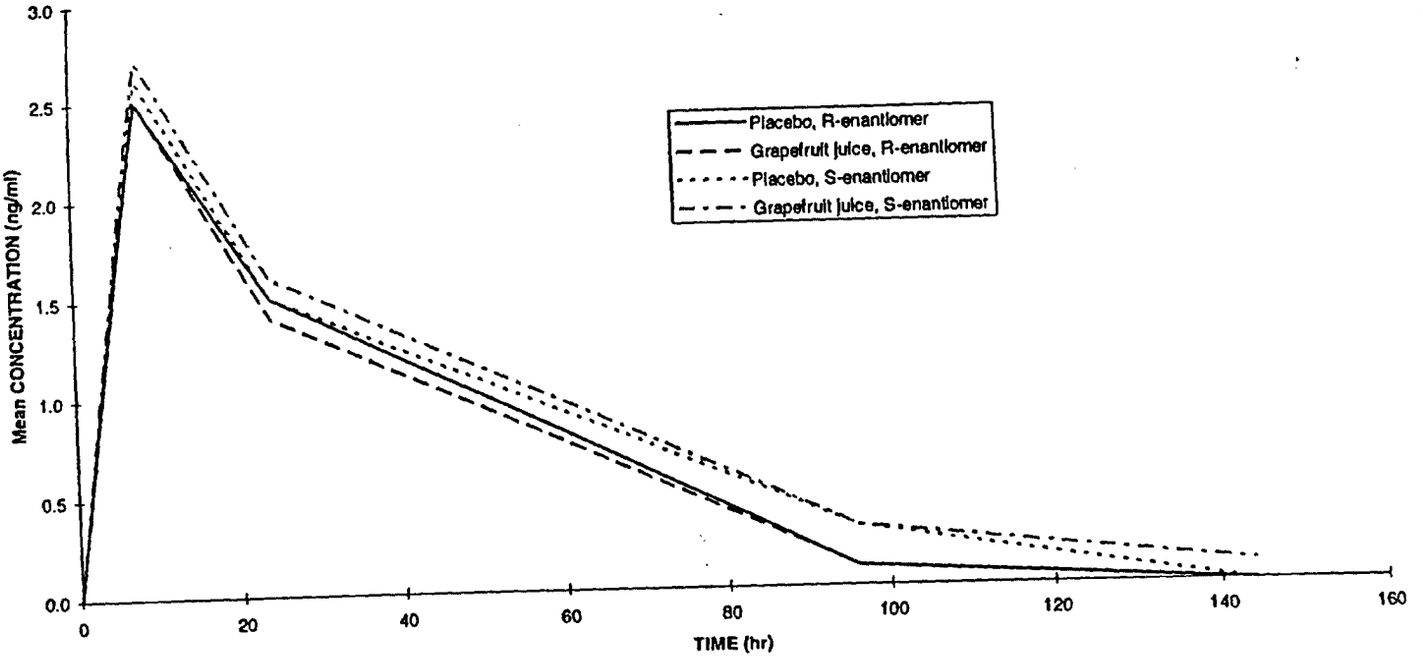

TABLE 5.3.1
AMLODIPINE PROTOCOL 053-017
SUMMARY OF STATISTICAL ANALYSES OF AMLODIPINE ENANTIOMER PARAMETERS - (SUBJECTS WITH FULL COMPLEMENT OF DATA)
IV ADMINISTRATION

PHARMACOKINETIC PARAMETER	JUICE	PLACEBO		95% CONFIDENCE INTERVAL
	GEOMETRIC MEAN		RATIO	
AUC (0-96) (ng.hr/ml)				
S	138.85	138.55	100.21%	(88.25%, 113.80%)
R	131.55	134.13	98.07%	(86.73%, 110.90%)
S/R	1.06	1.03	102.19%	(95.93%, 108.85%)
Cmax (ng/ml)				
S	12.38	16.65	74.36%	(57.85%, 95.59%)
R	13.04	17.24	75.65%	(58.84%, 97.26%)
S/R	0.95	0.97	98.30%	(94.39%, 102.37%)

Natural log-transformed AUC (0-24), AUC (0-96), Cmax, and C8 were analyzed. The anti-log (exponent) of the results was taken to estimate the ratios and the 95% confidence intervals of the ratios.

TABLE 5.3.2
AMLODIPINE PROTOCOL 053-017
SUMMARY OF STATISTICAL ANALYSES OF AMLODIPINE ENANTIOMER PARAMETERS - (SUBJECTS WITH FULL COMPLEMENT OF DATA)
ORAL ADMINISTRATION

PHARMACOKINETIC PARAMETER	JUICE	PLACEBO		95% CONFIDENCE INTERVAL
	GEOMETRIC MEAN		RATIO	
AUC (0-24) (ng.hr/ml)				
S	44.56	43.31	102.88%	(96.58%, 109.60%)
R	41.22	41.53	99.25%	(93.10%, 105.81%)
S/R	1.08	1.04	103.66%	(99.22%, 108.29%)
C8 (ng/ml)				
S	2.66	2.57	103.67%	(96.37%, 111.52%)
R	2.52	2.49	101.12%	(94.66%, 108.02%)
S/R	1.06	1.03	102.52%	(100.17%, 104.93%)

Natural log-transformed AUC (0-24), AUC (0-96), Cmax, and C8 were analyzed. The anti-log (exponent) of the results was taken to estimate the ratios and the 95% confidence intervals of the ratios.