

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19787/S17

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 19-787/S-017
S-020

JUL 12 2000

Pfizer Inc.
Attention: Ms. Rita A. Wittich
235 East 42nd Street
New York, New York 10017-5755

Dear Ms. Wittich:

Please refer to your supplemental new drug applications dated November 3, 1998 (S-017) and July 1, 1999 (S-020), received November 4, 1998 (S-017) and July 2, 1999 (S-020), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvasc (amlodipine besylate) Tablets.

We acknowledge receipt of your submission dated May 25, 2000. Your submission of May 25, 2000 constituted a complete response to our January 12, 2000 (S-017) and April 5, 2000 (S-020) action letter.

These supplemental new drug applications provide for final printed labeling revised as follows:

S-017

A **Geriatric Use** subsection was added to the **PRECAUTIONS** section:

Clinical studies of NORVASC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**).

S-020

The **PRECAUTIONS: Drug Interactions** subsection was revised to read as follows:

Drug Interactions: *In vitro* data in human plasma indicate that Norvasc has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Special Studies: Effect of other agents on Norvasc.

CIMETIDINE: Co-administration of Norvasc with cimetidine did not alter the pharmacokinetics of Norvasc.

GRAPEFRUIT JUICE: Co-administration of 240 mls of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

MAALOX (antacid): Co-administration of the antacid Maalox with a single dose of Norvasc had no effect on the pharmacokinetics of Norvasc.

SILDENAFIL: A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Norvasc. When Norvasc and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of Norvasc on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of Norvasc with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of Norvasc with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of Norvasc had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of Norvasc with warfarin did not change the warfarin prothrombin response time.

In clinical trials, Norvasc has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert contained in the submission dated May 25, 2000). Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Mr. David Roeder
Regulatory Project Manager
(301) 594-5332

Sincerely,

/s/ 7/12/00

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S17

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 19-787/S-020

APR 5 2000

Pfizer Inc.
Attention: Ms. Rita Wittich
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Wittich:

Please refer to your supplemental new drug application dated July 1, 1999, received July 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvasc (amlodipine besylate) Tablets.

This supplemental new drug application provides for draft labeling revised under **PRECAUTIONS: Drug Interactions**. The entire text of this subsection has been replaced with the following text:

Drug Interactions: *In vitro* data in human plasma indicate that Norvasc has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Special Studies: Effect of other agents on Norvasc.

CIMETIDINE: Co-administration of Norvasc with cimetidine did not alter the pharmacokinetics of Norvasc.

GRAPEFRUIT JUICE: Co-administration of 240 mls of grapefruit juice with a 10 mg oral dose of Norvasc or a 10 mg IV infusion of amlodipine had no effect on the pharmacokinetics of Norvasc.

MAALOX (antacid): Co-administration of the antacid Maalox with a single dose of Norvasc had no effect on the pharmacokinetics of Norvasc.

SILDENAFIL: A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Norvasc. When Norvasc and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of Norvasc on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of Norvasc with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of Norvasc with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of Norvasc had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of Norvasc with warfarin did not change the warfarin prothrombin response time.

In clinical trials, Norvasc has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

Please change the text regarding the interaction of amlodipine with grapefruit juice to read as follows:

GRAPEFRUIT JUICE: Co-administration of 240 mls of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy male volunteers had no significant effect on the pharmacokinetics of amlodipine.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

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If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110.

In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please call:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

RS/ 4/5/00

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S17

FINAL PRINTED LABELING

Labeling: original
NDA No. 19-787 Rfd. 5-26-00
Reviewed by: Beck 7-12-02

APPROVED

65-4782-00-9

Norvasc®

(amlodipine besylate)
Tablets

DESCRIPTION

NORVASC® is the besylate salt of amlodipine, a long-acting calcium channel blocker. NORVASC is chemically described as (R,S) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_5O_3S$, and its structural formula is:



Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. NORVASC (amlodipine besylate) tablets are formulated as white tablets equivalent to 2.5, 5 and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action: NORVASC is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that NORVASC binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. NORVASC inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by NORVASC. Within the physiologic pH range, NORVASC is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

NORVASC is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which NORVASC relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, NORVASC reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: NORVASC has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of NORVASC in vasospastic (Prinzmetal's or variant) angina.

Pharmacokinetics and Metabolism: After oral administration of therapeutic doses of NORVASC, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of NORVASC is not altered by the presence of food.

NORVASC is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of NORVASC are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of NORVASC are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Pharmacodynamics: Hemodynamics Following administration of therapeutic doses to patients with hypertension, NORVASC produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with NORVASC is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of NORVASC resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with NORVASC have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, NORVASC has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

CLINICAL PHARMACOLOGY (continued)

Studies in Patients with Congestive Heart Failure: NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of NORVASC 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, NORVASC had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on NORVASC and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Electrophysiologic Effects: NORVASC does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving NORVASC and concomitant beta blockers. In clinical studies in which NORVASC was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, NORVASC therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Effects in Hypertension: The antihypertensive efficacy of NORVASC has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on NORVASC and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Effects in Chronic Stable Angina: The effectiveness of 5-10 mg/day of NORVASC in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 NORVASC, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for NORVASC 10 mg, and averaged 7.9% (38 sec) for NORVASC 5 mg. NORVASC 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of NORVASC in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Effects in Vasospastic Angina: In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, NORVASC therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week (p<0.01). Two of 23 NORVASC and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

INDICATIONS AND USAGE

- 1. Hypertension**
NORVASC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
- 2. Chronic Stable Angina**
NORVASC is indicated for the treatment of chronic stable angina. NORVASC may be used alone or in combination with other antianginal agents.
- 3. Vasospastic Angina (Prinzmetal's or Variant Angina)**
NORVASC is indicated for the treatment of confirmed or suspected vasospastic angina. NORVASC may be used as monotherapy or in combination with other antianginal drugs.

CONTRAINDICATIONS

NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS

General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. NORVASC (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Special Studies: Effect of other agents on NORVASC.

CIMETIDINE: Co-administration of NORVASC with cimetidine did not alter the pharmacokinetics of NORVASC.

GRAPEFRUIT JUICE: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

MAALOX (antacid): Co-administration of the antacid Maalox with a single dose of NORVASC had no significant effect on the pharmacokinetics of NORVASC.

SILDENAFIL: A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of NORVASC. When NORVASC and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of NORVASC on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of NORVASC with 80 mg of atorvastatin resulted in no

PRECAUTIONS (continued)

significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of NORVASC had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of NORVASC with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis).

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m² basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on patient weight of 50 kg.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

Geriatric Use: Clinical studies of NORVASC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

	Placebo-Controlled Studies	
	NORVASC (%) (N=1730)	PLACEBO (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

ADR	NORVASC		PLACEBO	
	M=% (N=1218)	F=% (N=512)	M=% (N=914)	F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps,** myalgia.

Psychiatric: sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea,** epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

ADVERSE REACTIONS (continued)

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occurred in $\leq 0.1\%$ of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecostasia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE

Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

DOSEAGE AND ADMINISTRATION

The usual initial antihypertensive oral dose of NORVASC is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding NORVASC to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See ADVERSE REACTIONS section for information related to dosage and side effects.

Co-administration with Other Antihypertensive and/or Antianginal Drugs: NORVASC has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

HOW SUPPLIED

NORVASC® - 2.5 mg Tablets (amlodipine besylate equivalent to 2.5 mg of amlodipine per tablet) are supplied as white, diamond, flat-faced, beveled edged engraved with "NORVASC" on one side and "2.5" on the other side and supplied as follows:

NDC 0069-1520-68 Bottle of 90
NDC 0069-1520-66 Bottle of 100

NORVASC® - 5 mg Tablets (amlodipine besylate equivalent to 5 mg of amlodipine per tablet) are white, elongated octagon, flat-faced, beveled edged engraved with both "NORVASC" and "5" on one side and plain on the other side and supplied as follows:

NDC 0069-1530-68 Bottle of 90
NDC 0069-1530-66 Bottle of 100
NDC 0069-1530-41 Unit Dose package of 100
NDC 0069-1530-72 Bottle of 300

NORVASC® - 10 mg Tablets (amlodipine besylate equivalent to 10 mg of amlodipine per tablet) are white, round, flat-faced, beveled edged engraved with both "NORVASC" and "10" on one side and plain on the other side and supplied as follows:

NDC 0069-1540-68 Bottle of 90
NDC 0069-1540-66 Bottle of 100
NDC 0069-1540-41 Unit Dose package of 100

Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant containers (USP).

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Pfizer Labs

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Revised April 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19787/S17

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MAR 15 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-787 Serial No. ~~SLR~~ 020 SUBMISSION DATE: July 1, 1999
DRUG: Norvasc® 2.5, 5, 10 mg tablets
SPONSOR: Pfizer Pharmaceuticals Group REVIEWER: B. Nhi Nguyen, Pharm.D.

TYPE OF SUBMISSION: Supplemental NDA; labeling change; drug interaction

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BACKGROUND

Amlodipine is a dihydropyridine calcium antagonist approved in the US for the treatment of hypertension, chronic stable angina and vasospastic angina. Other calcium channel antagonists, that are substrates for cytochrome P450 3A4, have significant drug-drug and/or drug-grapefruit interactions. Amlodipine is extensively metabolised by the liver, but not specifically by 3A4. The sponsor conducted studies to define the drug-drug and drug-grapefruit interaction with amlodipine.

RECOMMENDATION

The studies submitted by the sponsor for NDA 19-787 are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The comments on page 5 should be adequately addressed by the sponsor.

SUMMARY OF SUBMISSION

Drug interactions

Maalox

Concomitant administration of 30 mL of Maalox® had no statistically or clinically significant effect on the disposition of amlodipine 5 mg.

Pharmacokinetic parameters between the two groups were similar. Mean C_{max} estimates were 2.23 ± 0.71 ng/mL vs. 2.22 ± 0.64 ng/mL, T_{max} estimates were 8 ± 2 hrs vs. 9 ± 2 hrs, and AUC₀₋₉₆ were 88.9 ± 30.8 ng*hr/mL vs. 89.5 ± 30.3 ng*hr/mL for without Maalox® vs. with Maalox®, respectively.

The ratio (with Maalox®/without Maalox®) of adjusted geometric means (90% CI) for AUC₀₋₉₆ (ng*hr/mL) was 101.2 % (95.1-107.6 %) and for C_{max} was 100.5 % (91.8-110 %). The 90% confidence limits of the difference between the two adjusted treatment means (with Maalox® - without Maalox®) for T_{max} were -0.37 hours to 1.59 hours.

Atorvastatin

The addition of amlodipine 10 mg daily to atorvastatin 80 mg daily showed no statistically significant effect on the pharmacokinetics of atorvastatin, nor was there any clinically important effects on the safety profile of atorvastatin.

The geometric mean AUC_(0-t) for atorvastatin equivalents administered with amlodipine was 1050 ng*hr/mL and 910 ng*hr/mL when administered with placebo. This AUC_(0-t) ratio of 116% had a 95% CI of 98%, 136%.

The geometric mean C_{max} for atorvastatin equivalents was 121 ng/mL when administered with amlodipine and 116 ng/mL when administered with placebo. This C_{max} ratio of 105% had a 95% CI of 84%, 131%.

The arithmetic mean T_{max} for atorvastatin equivalents when administered with amlodipine was 2.4 hours and 2 hours when given with placebo. The difference of 0.4 hours had a 95% CI of – 0.6 hours, 1.4 hours.

Amlodipine geometric mean AUC (232 ng*hr/mL) and T_{max} (8 hrs) when administered with atorvastatin are similar to that reported in other studies.

Ethanol

Single or multiple doses of amlodipine 10 mg does not have a significant effect on the pharmacokinetics of ethanol.

Single dose ethanol geometric mean AUC₍₀₋₈₎ was 4069 µg*h/mL from placebo vs. 4269 µg*h/mL from amlodipine. Single dose ethanol geometric C_{max} was 1012.5 µg/mL from placebo vs. 1046.1 µg/mL from amlodipine.

The 15 day ethanol geometric mean AUC₍₀₋₈₎ was 4150 µg*h/mL from placebo vs. 4448 µg*h/mL amlodipine 10 mg. The 15 day single dose ethanol geometric C_{max} was 1053.3 µg/mL from placebo vs. 1133.1 µg/mL from amlodipine.

Drowsiness and intoxications scale scores of subjects treated with amlodipine 10 mg daily tended to decrease compared to baseline (placebo followed by ethanol).

Grapefruit juice

Co-administration of 240 mls of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy male volunteers had no significant effect.

AUC_(0-∞) and C_{max} for oral or IV amlodipine was not affected by grapefruit juice. (See table. Data presented as mean ± SD.)

	AUC _(0-∞) (ng*hr/mL)	C _{max} (ng/mL)
Oral amlodipine		
With placebo	293 ± 58	5.8 ± 1.1
With grapefruit juice	315 ± 76	6.2 ± 1.1
IV amlodipine		
With placebo	358 ± 88	34.8 ± 13.7
With grapefruit juice	374 ± 88	30.1 ± 42.1

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

Sildenafil

A single dose of sildenafil 100 mg given to patients being treated with amlodipine for hypertension does not affect the AUC or Cmax of amlodipine. Tmax for amlodipine appears to be unaffected, however the confidence limits were wider.

COMMENTS TO THE MEDICAL OFFICER

Sildenafil

The medical officer is requested to determine whether the following statement concerning sildenafil is appropriate: "When Norvasc and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect."

COMMENTS TO BE SENT TO THE SPONSOR

The labeling revisions with regards to drug-drug interactions between amlodipine and antacids, atorvastatin, ethanol, and sildenafil are acceptable. However, with regards to grapefruit juice the package insert should read as follows:

Grapefruit juice

Co-administration of 240 mls of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy male volunteers had no significant effect on the pharmacokinetics of amlodipine.

Please forward the above comments to the sponsor.

ISI

3/15/00

B. Nhi Nguyen, Pharm.D.

RD/FT initialed by Patrick Marroum, Ph.D. */*

ISI

3/15/2000

cc: NDA 19-787, HFD-110 (Roeder), HFD-860 (Nguyen, Mehta), CDER central document room

APPENDIX I: STUDIES IN SUPPORT OF LABELING CHANGE

STUDY TITLE: Phase I study of the effects of concomitant antacid administration on the absorption of amlodipine

PROTOCOL 053-012

VOLUME: 57.2

PAGES: 1 - 216

INVESTIGATOR: {

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STUDY CENTER: L

J

STUDY DATES: January 24, 1990 – March 6, 1990

DESIGN: Open, randomized, two-way crossover

OBJECTIVES: To assess the effect of concomitant antacid Maalox® on the absorption of a single dose of amlodipine in normal male subjects

POPULATION: Normal male subjects between the ages of 18-45 years were recruited. All subjects were to weigh between 135 to 200 pounds and be within 10 % of ideal body weight.

FORMULATION:

- Maalox® suspension 30 ml containing AlOH 225mg/5mL and MgOH 200 mg/5mL (lot # 78957; FID# Rorer)
- Amlodipine 5 mg tablets (UK-48340-26; lot # 630-23; FID# 0735)

PROCEDURES:

Screening

All subjects had a complete history and physical, serum chemistries (including Anti-HBC, Anti-HBs, Anti-HAV), urine drug screen, ethanol breath test, and 12-lead EKG.

Subjects reported to the clinical research unit at least 12 hours prior to amlodipine dosing.

Dose

All doses were administered the morning after an 8 hour overnight fast. The two dosing days were separated by at least 14 days.

On day 1

- 14 of 27 subjects received only amlodipine 5 mg with 120 mL of water.
- The other 13 subjects received 30 mL of Maalox® prior to receiving amlodipine 5 mg. The antacid container was rinsed with two 30 mL of water and these were consumed by the subject. An additional 60 mL of water was administered with the amlodipine.

On day 15, each subject who remained in the study received the treatment not given on day 1.

For 4 hours after drug administration, subjects fasted, remained upright (except for blood pressure assessments), abstained from drinking caffeinated beverages and smoking. A standard meal was then consumed.

Blood samples for pharmacokinetic studies were collected as described below. Subjects were discharged after the 24-hour sample, but returned to the clinic for collection of the remaining blood samples.

Safety

Standing and supine blood pressure and pulse rate measurements were done at screening and at 1, 2, 6, 12, and 24 hours after receiving amlodipine. A standard 12-lead EKG was done at screening, prior to and 24 hours after receiving amlodipine.

PHARMACOKINETIC SAMPLING: Three milliliters of plasma were obtained from blood samples collected at the following time points: immediately prior to dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours after dosing. Plasma samples were kept at -20°C until analysis.

ASSAY:

Precision

The inter-day coefficient of variation (CV) ranged from 9.21 % to 10.5 %. Intra-day CV was not provided by the sponsor.

Accuracy

Inter-day accuracy was within 7.93 %. Intra-day accuracy was not provided by the sponsor.

Sensitivity

The lower limit of quantification, defined as the lowest non-zero plasma calibration level, was 0.200 ng/mL.

Linearity

The assay was linear over the range of _____ ng/mL. The average correlation coefficient was 0.9988.

Overall, the assay used to quantify amlodipine concentrations was acceptable.

ANALYSIS:

Pharmacokinetic

Plasma amlodipine concentration data were used to estimate pharmacokinetic parameters. These included AUC₀₋₉₆, C_{max}, and T_{max}.

The AUC was estimated using the linear trapezoidal method. The C_{max} was estimated directly from the experimental data with T_{max} defined as the first occurrence of C_{max}. Plasma concentrations < 0.2 ng/mL were assigned a value of 0.0 ng/mL for purposes of estimating the mean plasma concentrations at each sampling time and determining the AUC.

Statistical

Natural log-transformed AUC₀₋₉₆, C_{max}, and untransformed T_{max} values were analyzed using an ANOVA to test for sequence, subject within sequence, period, and treatment effects using PROC GLM in SAS. For AUC 0-96 and C_{max}, the anti-log of the differences and confidence limits was taken to estimate the ratio between treatment effects and the 90% confidence interval of the ratio. The pharmacokinetic parameters of amlodipine without concomitant Maalox® were used as the reference standards.

It was estimated that 24 subjects (12 in each treatment sequence group) were needed to detect a difference of 20% in the mean AUC for amlodipine alone and amlodipine with concomitant antacid with at least 80% power using a 5% significance level.

RESULTS:

Subjects

Twenty-seven subjects entered the study. They ranged in age from 19 to 42 years (mean age 29 years) and in weight from 62.3 to 92.1 kg (mean weight 79.1 kg). Twenty-three subjects were white. Three subjects discontinued for non-treatment-related reasons after receiving the first dose of amlodipine 5 mg. These subjects were excluded from the pharmacokinetic analysis.

Pharmacokinetic results:

Results are presented as mean ± SD. Twenty-four subjects were analyzed.

There were no significant differences in pharmacokinetic parameters between the two groups. See table 5.1 for each subject's pharmacokinetic parameters. Mean C_{max} estimates, t_{max}, and AUC₀₋₉₆ for the two treatment groups were similar as shown in the table below.

	Without Maalox®	With Maalox®
C _{max} (ng/mL)	2.23 ± 0.71	2.22 ± 0.64
T _{max} (hours)	8 ± 2	9 ± 2
AUC ₀₋₉₆ (ng*hr/mL)	88.9 ± 30.8	89.5 ± 30.3

There were no statistically significant sequence or period effects for AUC₀₋₉₆ or T_{max}, and no significant period effect for C_{max}. A statistically significant sequence effect was detected for C_{max}.

The plasma concentration time curve with and without Maalox® were almost identical. (See Figure 1.)

The ratio (with Maalox®/without Maalox®) of adjusted geometric means (90% CI) for AUC₀₋₉₆ (ng*hr/mL) was 101.2 % (95.1-107.6 %) and for C_{max} was 100.5 % (91.8-110 %). The 90% confidence limits of the difference between the two adjusted treatment means (with Maalox® - without Maalox®) for T_{max} were -0.37 hours to 1.59 hours.

Estimates of the terminal phase rate constant (K_{el}) could not be made for ~ 20% of the plasma concentrations versus time profiles examined because the length of the time interval over which quantifiable concentrations existed was too short relative to the projected half-life.

PROTOCOL DEVIATIONS: One subject was randomized to receive amlodipine first, but mistakenly received amlodipine with Maalox®. On day 15, he received amlodipine only. Thus, 11 subjects completed the treatment sequence of amlodipine → amlodipine with Maalox® and 13 subjects completed the treatment sequence amlodipine with Maalox® → amlodipine.

Three subjects weighed slightly more than the upper weight limit of 91 kg.

One subject used bacitracin, neomycin, and polymyxin B, received a tetanus vaccine, and took zinc during the study for scalp and knee wounds.

SAFETY: No serious adverse effects were reported. Three subjects discontinued the study for reasons unrelated to the study drug. Three subjects experienced side effects of mild to moderate severity considered to be possibly related to study drug (dizziness, headache).

CONCLUSION: Concomitant administration of 30 mL of Maalox® had no statistically or clinically significant effect on the disposition of amlodipine 5 mg.

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ON ORIGINAL**

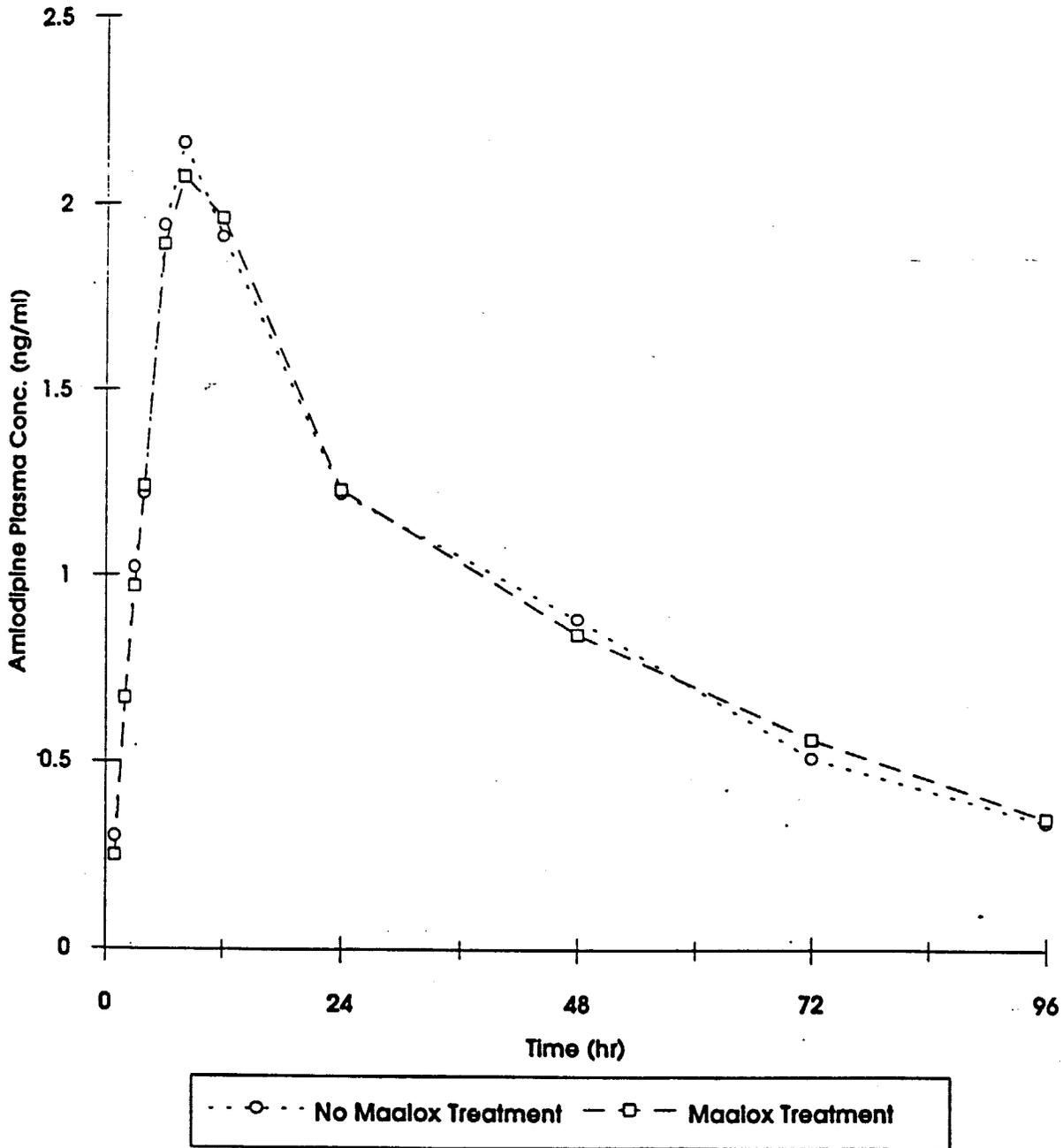
Table 5.1 Summary of Amlodipine Pharmacokinetic Parameters Determined Following Oral Administration of a Single 5 mg Dose With and Without Concomitant Maalox® Suspension (30 ml)
(Clinical Study #053-012-501,

Subj.	Seq. ^c	Cmax (ng/ml)		Tmax (hr)		AUC(0-96) (ng•hr/ml)	
		NM ^a	M ^b	NM	M	NM	M
501-0001	2						
501-0002	2						
501-0005	1						
501-0006	1						
501-0007	2						
501-0008	2						
501-0009	1						
501-0010	2						
501-0011	1						
501-0012	2						
501-0013	1						
501-0014	2						
501-0015	2						
501-0017	1						
501-0018	2						
501-0019	2						
501-0020	1						
501-0021	2						
501-0022	1						
501-0023	2						
501-0024	1						
501-0025	1						
501-0026	1						
501-0027	2						
Mean		2.23	2.22	8	9	88.9	89.5
S.D.		0.71	0.64	2	2	30.8	30.3

- a - No Maalox® treatment
- b - Maalox® treatment
- c - 1 = Amlodipine → Amlodipine + Maalox®
2 = Amlodipine + Maalox® → Amlodipine

Source Data: Appendix IIIA, Tables 1 and 2

Figure 1. Mean Plasma Concentrations of Amlodipine Following Oral Administration of a Single 5 mg Dose With and Without Concomitant Maalox Treatment (Clinical Study #053-012-501,



Source Data: Appendix IIIA, Tables 1 and 2

STUDY TITLE: The effect of amlodipine on the pharmacokinetics of atorvastatin in healthy adult male subjects

PROTOCOL 053-019

VOLUME: 57.4

PAGES: 1-251

INVESTIGATORS: ✓

STUDY CENTER: }
}

STUDY DATES: February 25, 1997 – April 21, 1997

DESIGN: randomized, open-label, placebo-controlled, two-treatment, two-period crossover study

OBJECTIVES: Examine the safety and tolerance of concurrent amlodipine and atorvastatin and to evaluate the effect of amlodipine on the pharmacokinetics of atorvastatin.

POPULATION: Sixteen healthy males (15 whites, 1 black) between the ages of 18 and 45 (mean 24 years old) entered and completed the study. Most were within 10% of ideal body weight (mean 79 kg). All subjects were nonsmokers and consumed no more than one alcohol unit per day.

FORMULATION:

Atorvastatin 40 mg tablets (Warner-Lambert, CG-0261096-G1)

Amlodipine 10 mg tablets (QC 1656, N3036)

Matching placebo tablets (WW-90-028, ED-G-163-595)

PROCEDURES:

Screening

Within 8 days prior to inclusion into the study, a complete medical history, physical exam and 12-lead ECG were obtained. Clinical chemistries, hematology, serum cotinine, urinalysis and drug screens were done.

Dose

A computer generated randomization schedule was used to assign subjects to one of two treatment sequences to be given as outpatients. Atorvastatin 80 mg daily was administered with either amlodipine 10 mg daily or with placebo for eight days. Subjects reported to the clinical research unit (CRU), received a standard breakfast at 0700 and were dosed at 0800. Following completion of the initial sequence (days 1-7) and a 14-day washout period (days 8-21), the other combination with atorvastatin was administered (days 22-28).

On days 8 and 29, subjects were admitted to the CRU at least 12 hours prior to dosing. Subjects fasted overnight and remained fasting for four hours following the dose. Blood samples were obtained for pharmacokinetic analysis at prespecified times for 24 hours following the dose on days 8 and 29. Blood pressure and pulse rate were determined at the same time as PK sampling. Lunch and dinner were provided at similar times on these two days.

Provisions

An ethanol breath test during each admission to the CRU was required to be negative.

If a subject discontinued from the study, the sponsor could elect to replace him with a substitute that would receive the same treatment allocation. All subjects who discontinued received a final physical examination.

Concomitant food/medications

Subjects were requested to avoid fruits and vegetables during the entire study. Consumption of grapefruit was not allowed from 48 hours before dosing to the end of the study. During the washout phase, subjects were instructed to abstain from alcohol, flavanoid containing foods and tobacco products.

No concomitant medications were taken during the study. Subjects were off all prescription drugs, OTC or recreational drugs for at least two weeks and off any investigational drug for at least four weeks prior to participating in the study.

Observed or volunteered adverse events were recorded throughout the study.

PHARMACOKINETIC SAMPLING: Prior to breakfast on days 1 and 22, a 10 mL baseline blood sample was drawn to provide a 5 mL plasma blank for the atorvastatin and amlodipine assays. On days 8 and 29, blood sufficient to provide at least 5 ml of plasma was collected and placed in heparinized tubes at times 0 (just prior to drug administration), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after drug administration.

ASSAY:

Precision

The inter-day CV for the calibration standards ranged from 2.26 - 10.2%. The intra-day CV was not provided by the sponsor.

Inter-day CV for the quality controls ranged from 3.45% (low control) to 7.34% (high control). Intra-day CV for the controls was not provided by the sponsor. Intra-day CV for the diluted quality control was 5.31%. Inter-day CV for the diluted quality control was not provided by the sponsor.

Accuracy

The inter-day relative error for the calibration standards was within 2.33%. Inter-day accuracy for the quality controls was within 8.57%. Intra-day accuracy for the diluted quality control was within 7.20%. Intra-day accuracy for the standards and controls was not provided by the sponsor.

Sensitivity

The lower limit of quantification, defined as the lowest concentration on a standard curve that can be measured with acceptable accuracy and precision, was 0.360 ng/mL with a standard deviation of 0.0115.

Linearity

The assay was linear up to 16.0 ng/mL.

Overall, the analytical assay for atorvastatin was acceptable.

AMLODIPINE

Quantification of amlodipine concentrations was determined by gas chromatography with electron-capture detection over the range of 0.2 ng/mL to 50 ng/mL.

Precision

The inter-day CV ranged from 3.04 % to 6.63 %. Intra-day CV was not provided by the sponsor.

Accuracy

Inter-day accuracy for the quality control pools was within 9.94 %. Intra-day accuracy was not provided by the sponsor.

Sensitivity

The lower limit of quantification, defined as the lowest non-zero plasma calibration level, was 0.200 ng/mL.

Linearity

The assay was linear over the range of 0.200 ng/mL to 50.0 ng/mL. The average correlation coefficient was 0.9995.

Overall, the analytical assay for amlodipine was acceptable.

ANALYSIS:**Pharmacokinetic**

The AUC for atorvastatin and amlodipine were calculated by the linear trapezoidal rule. C_{max} and T_{max} were obtained directly from the plasma concentration data.

Statistical

This study was designed to have at least 80% power at 5% level of significance to detect a 30% difference in atorvastatin AUC between the two regimens.

Natural log-transformed $AUC_{(0-t)}$ and C_{max} and untransformed T_{max} were analyzed using an ANOVA model containing sequence, subject within sequence, period and treatment effects. SAS procedure GLM with type III sums of squares was used for these analyses. Sequence effect was tested using mean square (MS) of subject within sequence as the error term while the period effect was tested using the within subject MSE as the error term. A 5% level of significance was used to test for these effects.

The LSMEANS statement of SAS was used to estimate the adjusted means and their variances and covariances. These were then used to estimate the adjusted mean difference between the treatment effects, their standard errors, and the 95% confidence intervals of the difference. For $AUC_{(0-t)}$ and C_{max} , the anti-log of the differences and confidence limits was taken to estimate the ratio between treatment effects and the 95% confidence interval of the ratio.

RESULTS:

Pharmacokinetic results

Individual and mean pharmacokinetic parameters for atorvastatin with amlodipine and with placebo are shown in Table 5.1. The geometric mean $AUC_{(0-t)}$ for atorvastatin equivalents administered with amlodipine was 1050 ng*hr/mL and 910 ng*hr/mL when administered with placebo (see also figure 1). This $AUC_{(0-t)}$ ratio of 116% had a 95% CI of 98%, 136%. The geometric mean C_{max} for atorvastatin equivalents was 121 ng/mL when administered with amlodipine and 116 ng/mL when administered with placebo. This C_{max} ratio of 105% had a 95% CI of 84%, 131%. The arithmetic mean T_{max} for atorvastatin equivalents when administered with amlodipine was 2.4 hours and 2 hours when given with placebo. The difference of 0.4 hours had a 95% CI of -0.6 hours, 1.4 hours.

Table 5.2 contains the individual and mean amlodipine pharmacokinetic parameters after coadministration with atorvastatin. Geometric mean AUC (232 ng*hr/mL) and T_{max} (8 hrs) are similar to that reported in other studies.

Safety results

There were no serious adverse events reported during the study. There were no treatment discontinuations or intercurrent illnesses.

Two subjects experienced five treatment related side effects and three subjects reported six all causality side effects while receiving atorvastatin/amlodipine. The side effects were all mild to moderate in severity with the exception of one severe headache.

Two subjects reported two treatment related side effects, and three subjects reported four all causality side effects while receiving atorvastatin/placebo. The treatment related side effects (headaches) were classified as moderate. The all causality side effects were mild to moderate in severity except for one severe postural dizziness.

CONCLUSION: The addition of amlodipine 10 mg daily to atorvastatin 90 mg daily showed no statistically significant effect on the pharmacokinetics of atorvastatin, nor was there any clinically important effects on the safety profile of atorvastatin.

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ON ORIGINAL**

Table 5.1 Individual and Mean Pharmacokinetic Parameters for Atorvastatin 80 mg Following Coadministration with Placebo or with 10 mg Amlodipine Tablets

Amlodipine Protocol No.: 053-019

Subject #	AUC 0-Tlast	AUC0-Tlast	Cmax	Cmax	Tmax	Tmax
	(ng*hr/ml)	(ng*hr/ml)	(ng/ml)	(ng/ml)	(hr)	(hr)
	WITH		WITH		WITH	
	WITH PLACEBO	AMLODIPINE	WITH PLACEBO	AMLODIPINE	WITH PLACEBO	AMLODIPINE
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
Mean ^a	987	1120	129	131	2.0	2.4
S.D.	428	395	62.3	55.5	1.1	1.1
%CV	43	35	48	42	54	48
Geometric Mean	910	1050	116	121	n/a	n/a

^aArithmetic Means

Source data: Appendix IIIA, Tables 1 and 2

3/30/98

Table 5.2 Individual and Mean Pharmacokinetic Parameters for Amlodipine on Day 8
Following Coadministration with 80 mg Atorvastatin Tablets

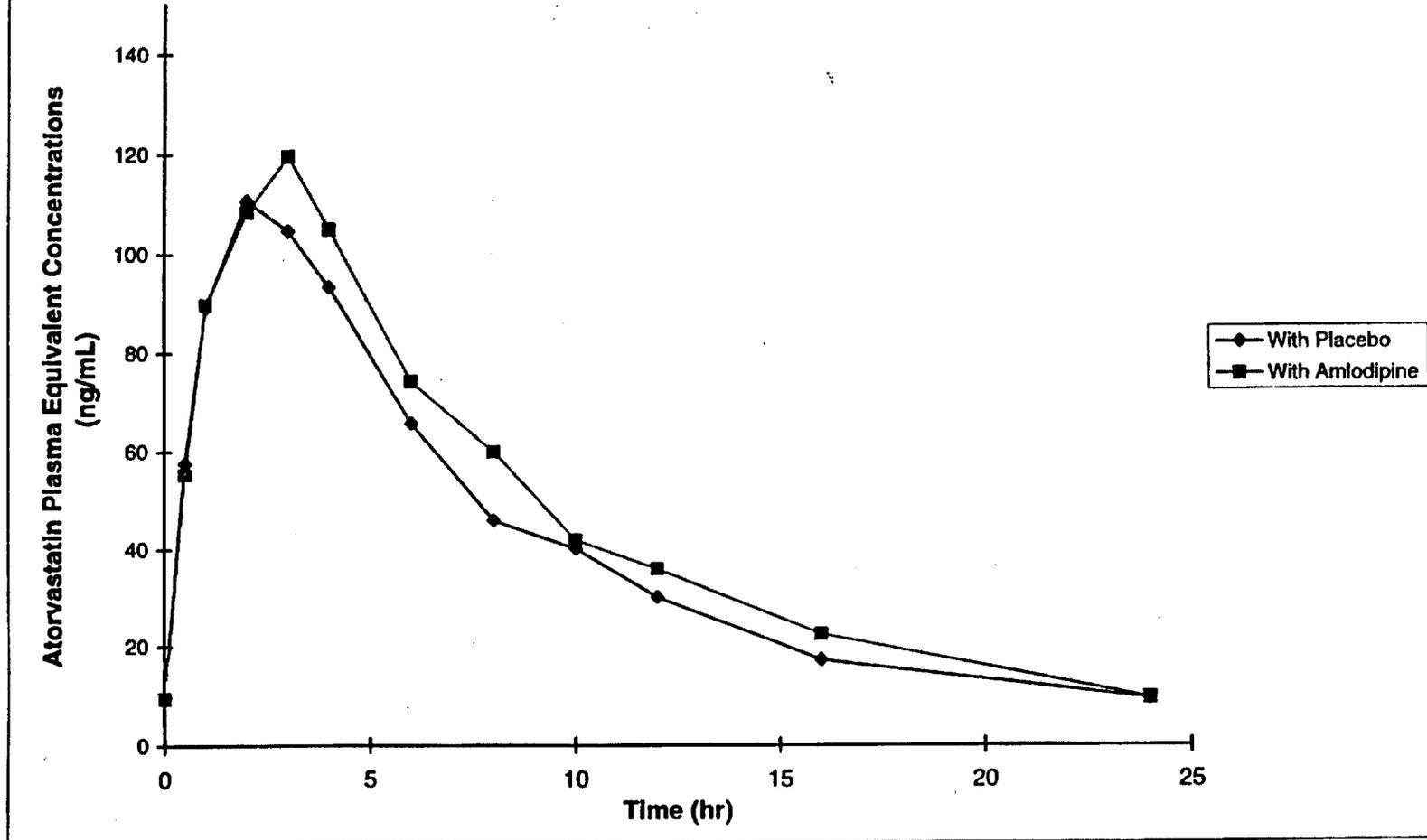
Amlodipine Protocol No.: 053-019

Subject #	AUC _{0-Tlast} (ng*hr/ml)	C _{max} (ng/ml)	T _{max} (hr)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
Mean ^a	238	12.0	8.0
S.D.	58.9	3.1	1.7
%CV	29.2	31.8	21.1
Geometric Mean	232	11.7	7.9

^aArithmetic Means

Source data: Appendix IIIA, Table 3

Figure 1. Mean Plasma Atorvastatin Equivalent Concentrations vs. Time Following Coadministration With and Without 10 mg Amlodipine



Source of Data: Appendix IIIA, Tables 1 and 2.

3/30/98

JUN 25 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-787 B002
Letter Date: July 11th, 1996
Drug: Amlodipine besylate (Norvasc)
Sponsor: Pfizer

Reviewer: Nakissa Sadrieh Ph.D.

Re: "A single blind, parallel group study of the effects of single and multiple doses of amlodipine, lisinopril, diltiazem and simvastatin on the pharmacokinetics of alcohol in normal volunteers." Protocol 053-016 study report.

Background:

It has been reported that a patient who was taking a combination of lisinopril, amlodipine and simvastatin (20 mg daily), exhibited very high blood alcohol levels suggestive of a drug interaction. It was however not clear which of the drugs the patient was taking was responsible for the interaction with alcohol, since there have been no previous interaction studies with alcohol, involving any of these drugs. Additionally, it has been reported that verapamil inhibits ethanol elimination in man.

Amlodipine is a calcium channel blocker of the 1,4-dihydropyridine family. It is approved in the US for the treatment of angina pectoris and mild to moderate essential hypertension.

Lisinopril is a synthetic peptide derivative long-acting angiotensin converting enzyme inhibitor that lowers blood pressure by inhibiting the renin-angiotensin-aldosterone system. Lisinopril is excreted unchanged in the urine. It is approved for the treatment of hypertension in the US.

Simvastatin is a methylated derivative of lovastatin which is a cholesterol lowering agent. It consists of a lactone which is hydrolyzed in vivo to its major active β -hydroxyacid metabolite, an HMG-CoA reductase inhibitor. Simvastatin undergoes extensive hepatic first pass metabolism where its active metabolite is preferentially concentrated. It is approved in the US to treat hypercholesterolemia.

Diltiazem is a benzothiazepin derivative calcium channel blocker approved in the US for the treatment of hypertension and angina pectoris. Diltiazem has a short elimination

$t_{1/2}$ thus necessitating frequent dosing in man. However, upon increased dosing, the terminal $t_{1/2}$ increases, due to the non-linear PK characteristics of the drug. Diltiazem is extensively metabolized by CYP 3A and its major metabolite (N-demethyldiltiazem) has pharmacological activity in man. Diltiazem is a competitive inhibitor of cyclosporine and propranolol.

The present study is aimed at reproducing the reported effect using amlodipine, lisinopril and simvastatin administered at a single dose and as multiple doses. Additionally, the effects of single and multiple doses of amlodipine and diltiazem are studied on the disposition of ethanol.

Results:

The pharmacokinetic parameters for ethanol are summarized in table 4.1.5 and the PK parameters for amlodipine are summarized in table 4.1.6.

The full model ANOVA indicated that there were no significant treatment group, period, or group*period interaction effects for ethanol AUC (0-8), C_{max} or T_{max} . When compared to baseline (placebo followed by ethanol), only single dose administration of diltiazem (120 mg) followed by ethanol ingestion resulted in a statistically higher mean AUC(0-8) estimate versus that obtained with single dose amlodipine (10 mg) and ethanol.

For amlodipine, no significant differences were noted between the 7-day and 15-day estimates. Mean systemic exposure to S- amlodipine was greater than that for R- amlodipine following multiple dose treatment by approximately 20% for both the amlodipine and combination treatment groups. Mean exposure of both enantiomers following single dose treatment was similar between the groups. The S-:R- ratio was generally 1.0 on day 7 and 1.2 on day 15 for both C_{max} and AUC(0-12). The amlodipine S-:R- AUC(0-12) ratio was plotted against the ethanol AUC(0-8) for the combination and amlodipine groups for both the single and multiple dose groups. No relationship was apparent.

None of the treatment groups were significantly different from placebo in their effect on supine blood pressure, diastolic blood pressure and pulse.

After both single dosing (day 7) and multiple dosing (day 15), the drowsiness and intoxication scale scores of subjects treated with either amlodipine or with combination treatment, tended to decrease from baseline. The mean percentage changes from baseline in total intoxication score over time for subjects treated with amlodipine were -11% and -23% for single and multiple dosing, respectively. For the subjects treated with the combination of drugs, the percentage change from baseline in the intoxication score was -8% and -17% following single and multiple dosing, respectively.

The mean percentage changes from baseline in total drowsiness score over time for subjects treated with amlodipine were approximately -4% following both single and multiple dosing. For the subjects treated with the combination, the mean percent change in the drowsiness score over time was approximately 1% following both single and multiple dosing. However, none of the changes in score were significantly different from those observed in subjects treated with placebo.

Subjects treated with diltiazem had increases in intoxication and drowsiness scores above baseline following single and multiple dosing. However, the only differences relative to placebo that were statistically significant were in total drowsiness score over time after both single and multiple dosing (12% and 15%, respectively).

When compared to amlodipine or combination treatment, the intoxication scores for the diltiazem group were significantly higher following multiple dosing and the drowsiness scores for the diltiazem group were significantly higher for both single and multiple dosings. *This data is in accordance with the finding that diltiazem treatment followed by ethanol resulted in higher AUC for ethanol as compared to amlodipine treatment followed by ethanol treatment.*

It is concluded that there is no effect of amlodipine either alone or in combination with simvastatin and lisinopril on the PK of ethanol in healthy male volunteers.

Comments: These results do not provide additional information which could be included in the package insert.

Recommendations: No further action is recommended at this time.

RD/FT initialed by Patrick Marroum, Ph.D.

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6/25/98
Nakissa Sadrieh, Ph.D.
6/25/1998

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

Appendix 1

A single blind, parallel group study of the effects of single and multiple doses of amlodipine, lisinopril, diltiazem and simvastatin on the pharmacokinetics of alcohol in normal volunteers.

Study No. 053-016

Volume 1.1-2

Pages 1-771

Study initiated April 26th, 1993
Study completed June 28th, 1993

Investigators:

Objectives:

1. To investigate the effect of single and multiple doses of amlodipine on the PK of ethanol.
2. To assess the effect of single and multiple doses of diltiazem on the PK of ethanol.
3. To evaluate the effect of co-administration of a combination of single and multiple doses of amlodipine, lisinopril and simvastatin on the PK of ethanol.
4. To examine the effect of these interactions on some simple measures of psychological evaluation (self-rated intoxication and drowsiness score).

Medication and dose level:

Amlodipine 10 mg tablets (FID #WW-89-018, lot number ED-G-014-190)
Diltiazem 120 mg tablets (lot number ED-0-44-293)
Lisinopril 20 mg tablets (lot number ED-0-043-293)
Simvastatin 40 mg tablets (lot number ED-0-042-293)
Matching placebo tablets (FID #QC 1657, lot number CO215-QC1567)

Study population:

Healthy male volunteers between the ages of 21 and 45 years with social drinking habits (less than or equal to 2 alcoholic beverages per day). Ten males are included in each group. Three subjects dropped out from the placebo group, but were replaced with other subjects.

Design:

This was a placebo-controlled, single-blind, randomized, parallel group study of single and multiple doses of amlodipine, either alone or in combination with simvastatin and lisinopril. Subjects were assigned to one of 4 treatment groups:

Group A: combination treatment (amlodipine 10 mg, lisinopril 20 mg, simvastatin 40 mg) once daily.

Group B: placebo 3 times daily.

Group C: amlodipine 10 mg once daily.

Group D: diltiazem 120 mg 3 times daily.

On day 1, all subjects were to take 1 placebo tablet at 7:00 and then ingest a single dose of ethanol (0.8 g/kg) 2 hours later.

On days 2-6, all subjects were to take 1 placebo tablet in the morning.

On day 7 (single dose assessment), subjects were to receive a single dose according to their group randomization at 7:00 am, and were then to ingest a single dose of ethanol 2 hours later.

On days 8-14, subjects were to receive study drug.

On day 15 (multiple dose assessment), subjects were to receive the morning dose as on days 8-14, and were to ingest a single dose of ethanol 2 hours later.

Please refer to the scheme of the study design which is enclosed in attachment 1.

Subjects were fasted for 8 hours prior to drug administration and for 4 hours following drug administration. A standard meal was to be served subsequently (composition not described). Study drug or placebo were administered with 240 ml water and ethanol was supplied as a 20% solution in orange juice.

Pharmacokinetic sampling:

Venous blood specimens were obtained for ethanol pharmacokinetic studies at the following time points:

2 hours pre-dose, just prior to dosing, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours after dosing on days 1, 7 and 15.

Additionally, blood was also collected from the subjects in group A (combination) and group C (amlodipine) for the determination of plasma amlodipine levels. Sampling was done at the following time points:

Immediately prior to dosing, 2, 3, 4, 6, 8, 10, 12, 14, 18 and 26 hours after amlodipine administration on days 7 and 15.

Pharmacodynamic measures were to be based on changes in supine blood pressure and heart rate. Subjective psychological performance was to be assessed by means of a Visual Analogue Scale and a Drowsiness scale administered on days 1, 7 and 15.

Assay procedures:

Data analysis:

The concentrations of ethanol were quantifiable ($2.8 \mu\text{g/ml}$ or greater) out to only 8 hours post ethanol ingestion, therefore the AUC (0-8 hours) was determined. The AUC (0-12 hours) was determined for R- and S- amlodipine. C_{max} and T_{max} were also determined.

Statistical analysis using ANOVA was performed to test for an overall period effect between days 1, 7 and 15 for ethanol AUC, Cmax and Tmax.

Results:

The pharmacokinetic parameters for ethanol are summarized in table 4.1.5 and the PK parameters for amlodipine are summarized in table 4.1.6. Additionally, please find enclosed a copy of the plasma concentration time profiles.

The full model ANOVA indicated that there were no significant treatment group, period, or group*period interaction effects for ethanol AUC (0-8), Cmax or Tmax. When compared to baseline (placebo followed by ethanol), only single dose administration of diltiazem (120 mg) followed by ethanol ingestion resulted in a statistically higher mean AUC(0-8) estimate versus that obtained with single dose amlodipine (10 mg) and ethanol.

For amlodipine, no significant differences were noted between the 7-day and 15-day estimates. Mean systemic exposure to S- amlodipine was greater than that for R- amlodipine following multiple dose treatment by approximately 20% for both the amlodipine and combination treatment groups. Mean exposure of both enantiomers following single dose treatment was similar between the groups. The S-:R- ratio was generally 1.0 on day 7 and 1.2 on day 15 for both Cmax and AUC(0-12). The amlodipine S-:R- AUC(0-12) ratio was plotted against the ethanol AUC(0-8) for the combination and amlodipine groups for both the single and multiple dose groups. No relationship was apparent.

None of the treatment groups were significantly different from placebo in their effect on supine blood pressure, diastolic blood pressure and pulse.

After both single dosing (day 7) and multiple dosing (day 15), the drowsiness and intoxication scale scores of subjects treated with either amlodipine or with combination treatment, tended to decrease from baseline. The mean percentage changes from baseline in total intoxication score over time for subjects treated with amlodipine were -11% and -23% for single and multiple dosing, respectively. For the subjects treated with the combination of drugs, the percentage change from baseline in the intoxication score was -8% and -17% following single and multiple dosing, respectively.

The mean percentage changes from baseline in total drowsiness score over time for subjects treated with amlodipine were approximately -4% following both single and multiple dosing. For the subjects treated with the combination, the mean percent change in the drowsiness score over time was approximately 1% following both single and multiple dosing. However, none of the changes in score were significantly different from those observed in subjects treated with placebo.

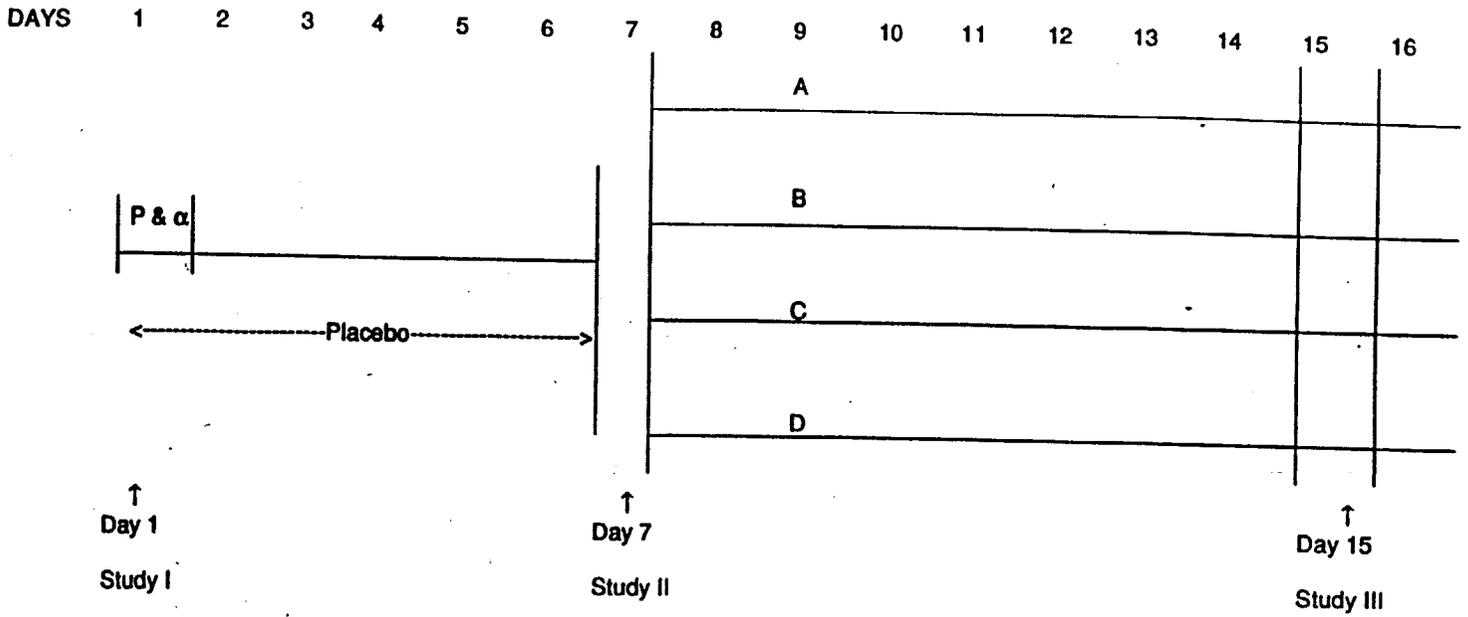
Subjects treated with diltiazem had increases in intoxication and drowsiness scores above baseline following single and multiple dosing. However, the only differences relative to placebo that were statistically significant were in total drowsiness score over time after both single and multiple dosing (12% and 15%, respectively).

When compared to amlodipine or combination treatment, the intoxication scores for the diltiazem group were significantly higher following multiple dosing and the drowsiness scores for the diltiazem group were significantly higher for both single and multiple dosings. *This data is in accordance with the finding that diltiazem treatment followed by ethanol resulted in higher AUC for ethanol as compared to amlodipine treatment followed by ethanol treatment.*

It is concluded that there is no effect of amlodipine either alone or in combination with simvastatin and lisinopril on the PK of ethanol in healthy male volunteers.

**APPEARS THIS WAY
ON ORIGINAL**

Attachment # 1 (Study Scheme)



Treatments

A = amlodipine, lisinopril, simvastatin

lacebo

C = amlodipine

D = diltiazem

P & α = placebo and alcohol

Table 4.1.5. Summary of Ethanol Pharmacokinetic Estimates Following Single Oral Doses of a 20% Ethanol Solution (0.8 g/kg) Ingested After Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Oral Doses of the Respective Treatments in Healthy Male Volunteers.
(Clinical Study # 053-016-599,

Treatment Group ^a	Day ^b	N	AUC(0-8) (µg·h/ml)		C _{max} (µg/ml)		T _{max} (h)
			Arithmetic Mean (SD)	Geometric Mean	Arithmetic Mean (SD)	Geometric Mean	
Combination)	A	10	3980 (665)	3925	1001.5 (173.4)	986.3	1.4 (0.5)
	7	10	4246 (655)	4200	1089.2 (162.5)	1077.4	1.3 (0.5)
	15	10	4227 (720)	4173	1078.0 (151.8)	1068.4	1.2 (0.4)
placebo)	B	10	4164 (907)	4069	1029.3 (193.8)	1012.5	1.4 (0.4)
	7	10	4292 (722)	4236	1080.6 (162.8)	1069.5	1.2 (0.5)
	15	10	4225 (801)	4150	1063.0 (148.0)	1053.3	1.1 (0.3)
amlodipine)	C	10	4314 (629)	4269	1051.1 (107.1)	1046.1	1.2 (0.4)
	7	10	4335 (560)	4301	1080.2 (149.1)	1070.9	1.2 (0.5)
	15	10	4534 (976)	4448	1139.6 (132.8)	1133.1	1.0 (0.3)
diltiazem)	D	10	3948 (569)	3913	982.1 (126.9)	974.3	1.5 (0.5)
	7	10	4482 (558)	4452	1042.6 (87.3)	1039.3	1.4 (0.7)
	15	10	4167 (554)	4122	1063.2 (160.8)	1034.2	1.7 (0.6)

^aA = Amlodipine 10 mg qd, Lisinopril 20 mg qd, Simvastatin 40 mg qd
^B = Placebo tid
^C = Amlodipine 10 mg qd
^D = Diltiazem 120 mg tid

^bDay 1 = Placebo administration to all subjects in all treatment groups followed by ethanol 2 hours post placebo
 Day 7 = Single dose administration followed by ethanol at 2 hours post-dose.
 Day 15 = Multiple dose administration (i.e., from Day 8) followed by ethanol at 2 hours post-dose.

Table 4.1.6. Summary of R(+) and S(-) Amlodipine Pharmacokinetic Estimates Following Single (Day 7) and Multiple Doses (Day 15) of the Respective Treatments and a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) in Healthy Male Subjects. (Clinical Study # 053-016-599,

Treatment Group ^a	Day ^b	N		AUC(0-12) ($\mu\text{g}\cdot\text{h}/\text{ml}$)		C _{max} ($\mu\text{g}/\text{ml}$)		T _{max} (h)		S(-):R(+)	
				R(+)	S(-)	R(+)	S(-)	R(+)	S(-)	AUC(0-12)	C _{max}
(Combination) A	7	10	Arithmetic Mean	20.2	20.1	2.39	2.40	8.8	9.2	1.006	1.005
			(SD)	7.1	6.6	0.75	0.73	1.7	1.9	0.083	0.066
			Geometric Mean	19.0	19.0	2.28	2.29	--	--	1.003	1.003
A	15	10	Arithmetic Mean	69.7	80.9	6.97	8.34	7.0	7.4	1.192	1.237
			(SD)	28.3	29.2	2.75	2.6	2.2	1.9	0.274	0.231
			Geometric Mean	64.6	75.2	6.5	7.92	--	--	1.164	1.218
(Amlodipine) C	7	9	Arithmetic Mean	19.0	19.4	2.27	2.30	6.7	6.2	1.031	1.017
			(SD)	5.8	5.0	0.70	0.65	2.0	2.1	0.064	0.054
			Geometric Mean	18.3	18.8	2.18	2.22	--	--	1.029	1.015
C	15	10	Arithmetic Mean	72.7	89.5	6.99	8.85	7.8	8.8	1.250	1.278
			(SD)	22.3	26.5	2.02	2.66	3.0	2.5	0.170	0.170
			Geometric Mean	69.2	85.8	6.68	8.47	--	--	1.240	1.268

^aA = Amlodipine 10 mg qd, Lisinopril 20 mg qd, Simvastatin 40 mg qd
^cC = Amlodipine 10 mg qd

^bDay 7 = Single dose administration followed by ethanol at 2 hours postdose.
 Day 15 = Multiple dose administration (i.e., from Day 8) followed by ethanol at 2 hours postdose.

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Figure 13. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Daily Oral Doses of Amlodipine 10 mg, Lisinopril 20 mg, and Simvastatin 40 mg to the Healthy Male Subjects in Group A (Clinical Study #053-016-599,

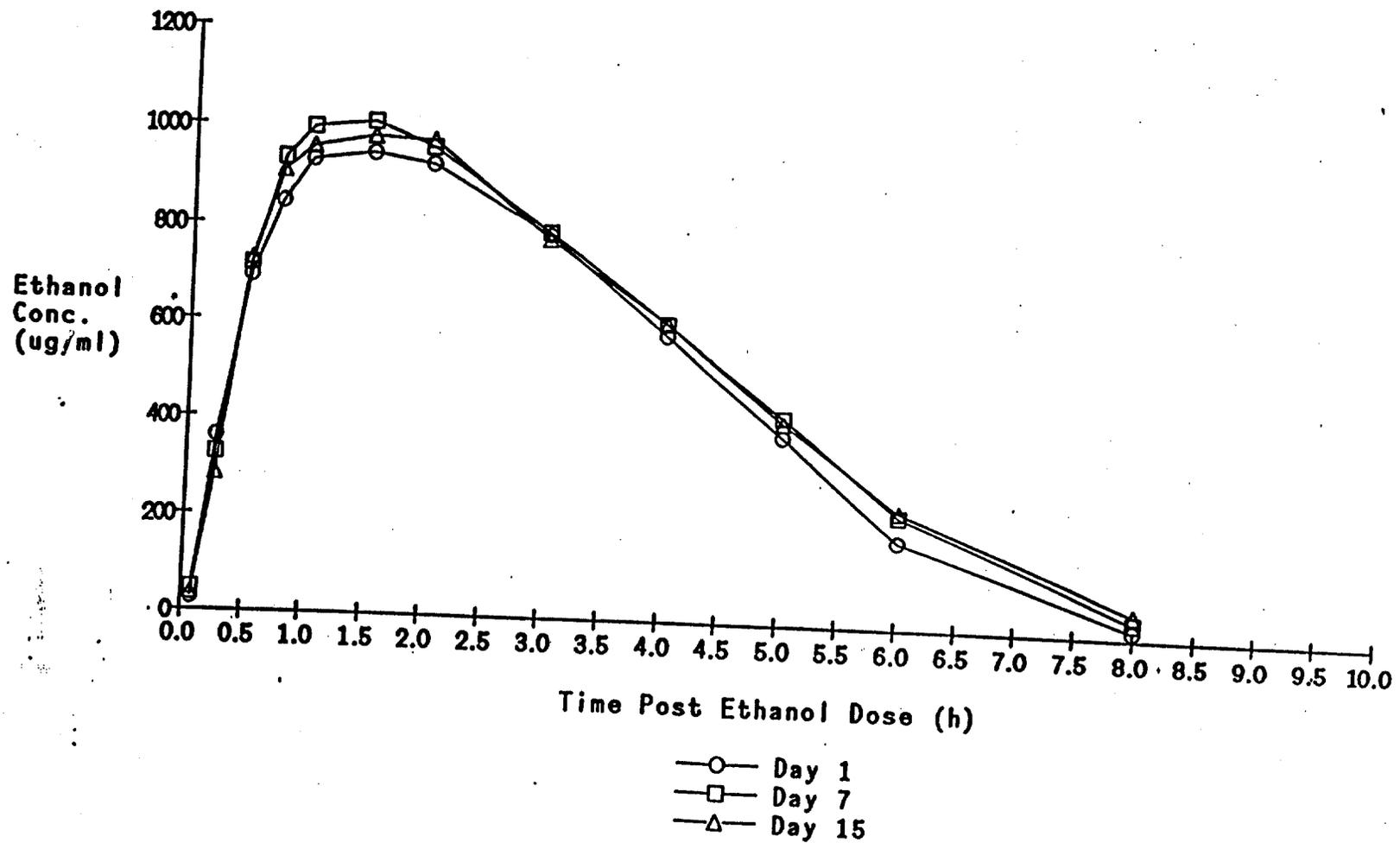
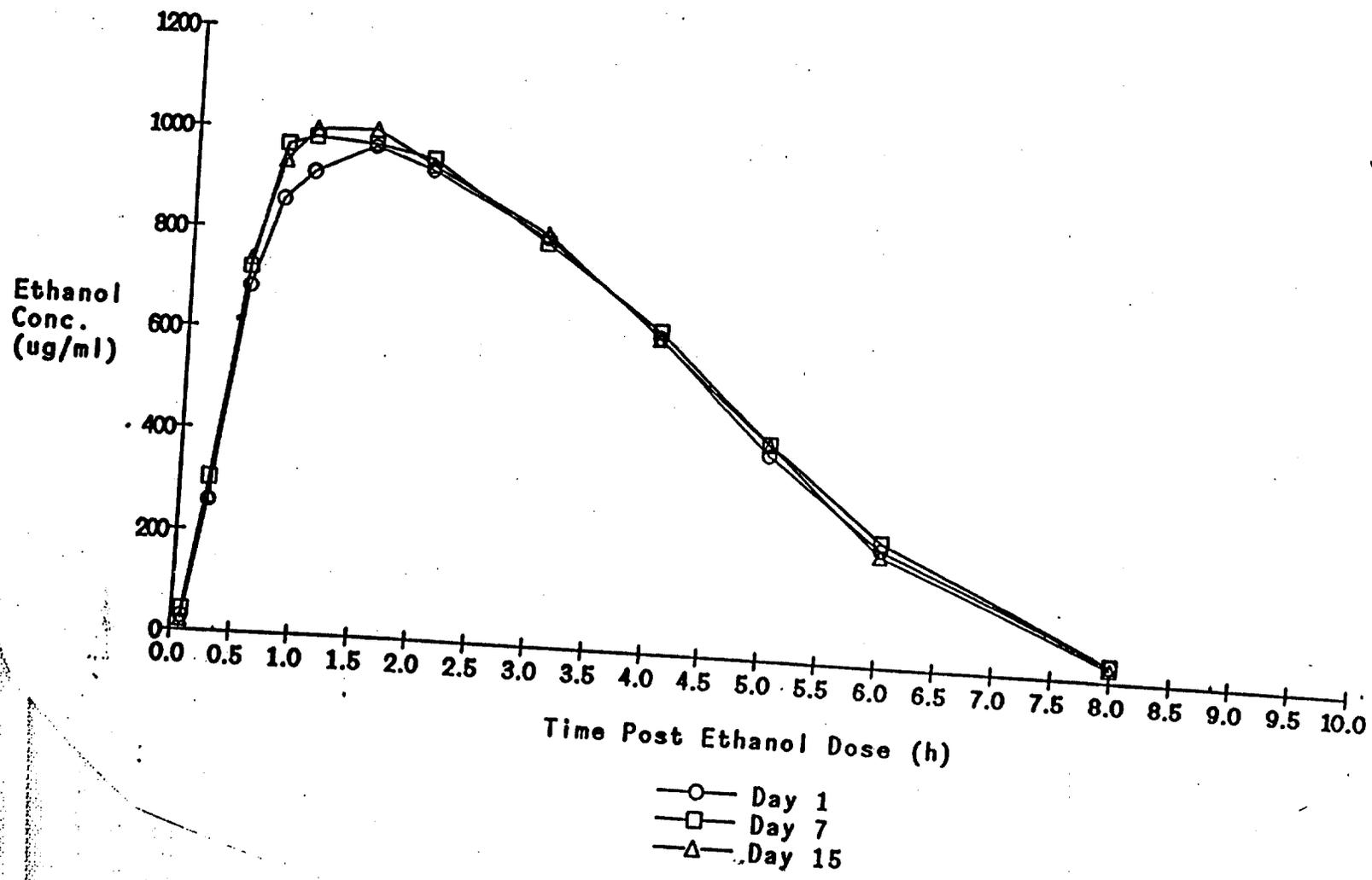


Figure 14. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Daily Oral Doses of Placebo to the Healthy Male Subjects in Group B (Clinical Study #053-016-599,



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Figure 15. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Daily Oral Doses of Amlodipine 10 mg to the Healthy Male Subjects in Group C (Clinical Study #053-016-599,

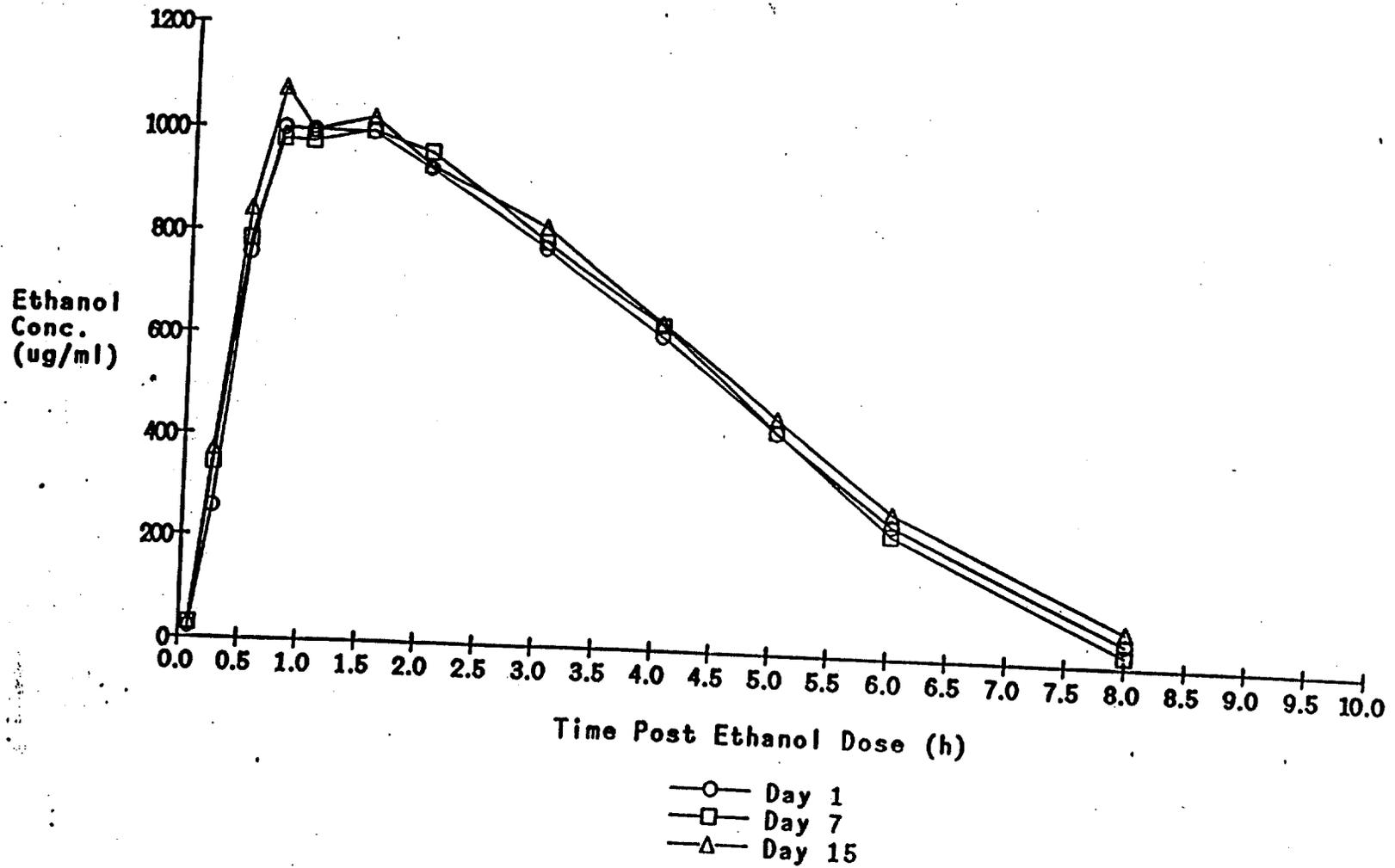


Figure 16. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Oral Doses of Diltiazem 120 mg to the Healthy Male Subjects in Group D (Clinical Study #053-016-599,

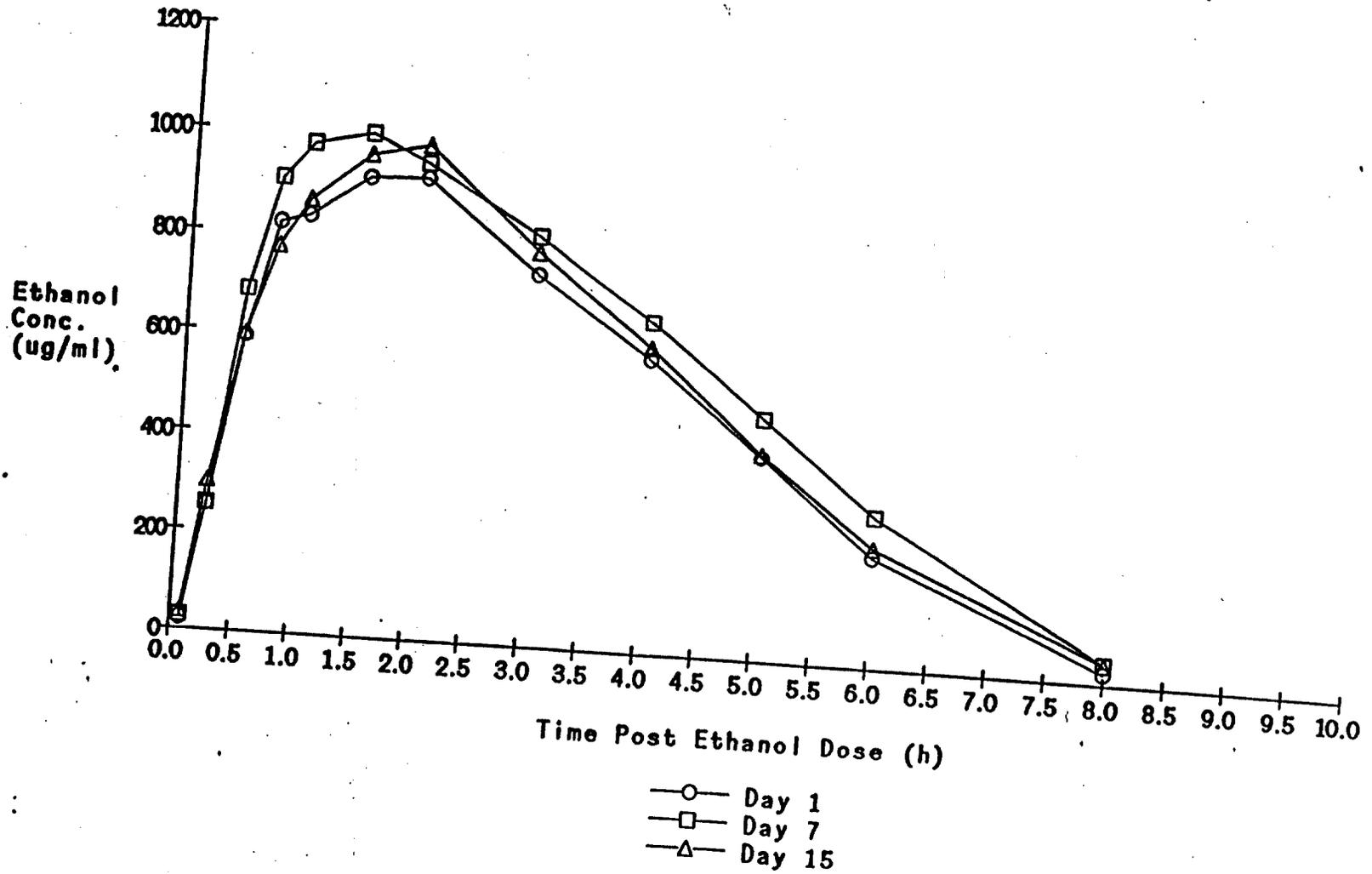
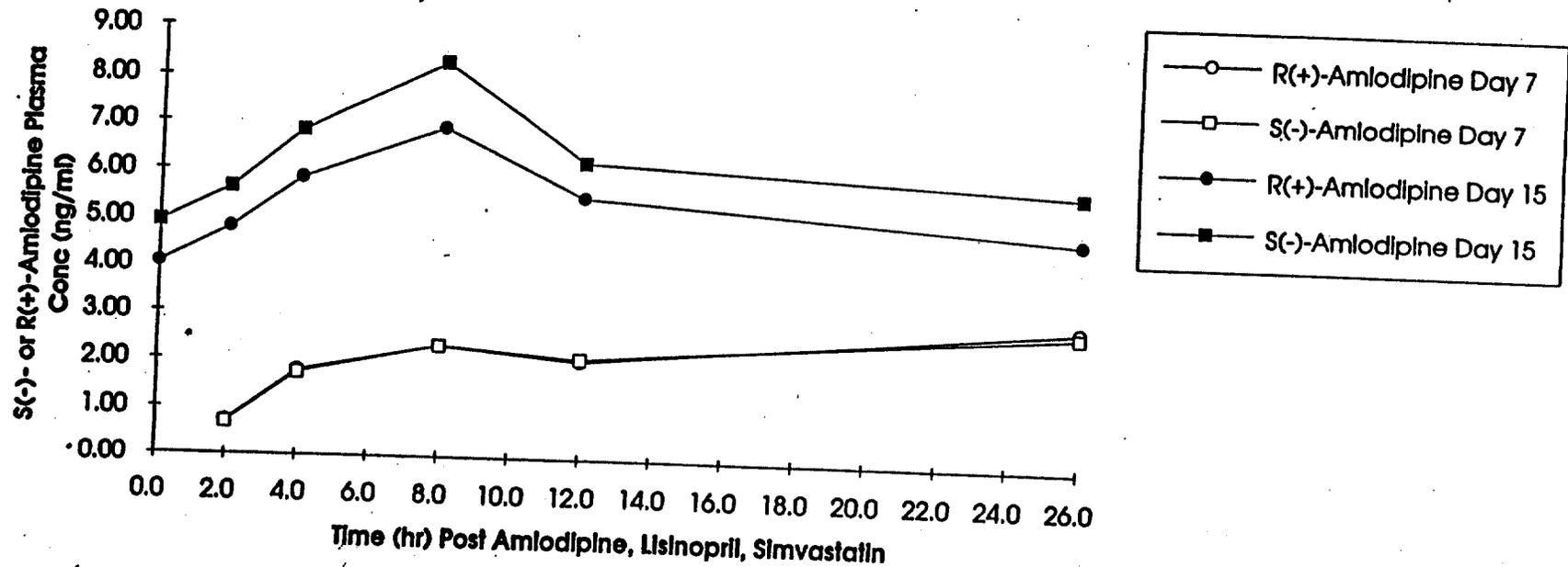


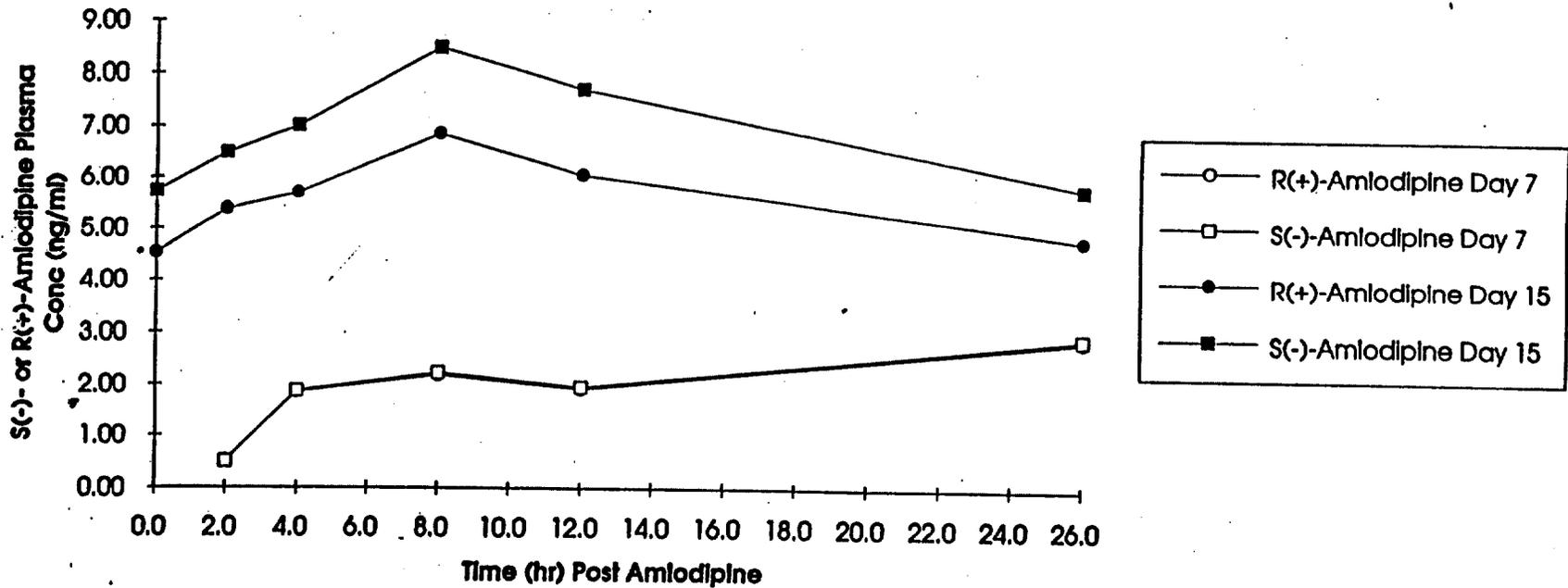
Figure 25. Mean Amlodipine Enantiomer Concentrations Following Ingestion of a 20% Ethanol Solution at 2 Hours After Single (Day 7) and Multiple (Day 15) Doses of Amlodipine 10 mg, Lisinopril 20 mg, Simvastatin 40 mg to Healthy Male Subjects (Group A)

(Clinical Study #053-016-599,



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Figure 26. Mean Amlodipine Enantiomer Concentrations Following Ingestion of a 20% Ethanol Solution at 2 Hours After Single (Day 7) and Multiple (Day 15) Doses of Amlodipine 10 mg to Healthy Male Subjects (Group C) (Clinical Study #053-016-599,



Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-787 N (IM) 633
Letter Date: April 5th, 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 C_{max} 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 C_{max} values of the R- and S- enantiomers after IV dosing and grapefruit juice showed a decrease of 24% and 26% for C_{max}, as compared to the C_{max} 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/

Nakissa Sadrieh, Ph.D.

7/2/98

RD/FT initialed by Patrick Marroum, Ph.D. _____

/S/

7/9/98

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

**APPEARS THIS WAY
ON ORIGINAL**

Appendix 1

The effect of grapefruit juice 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 concentration.

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, additional 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 $t_{1/2}$, were determined. Natural log-transformed AUC, Cmax, and absolute bioavailability (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.

**APPEARS THIS WAY
ON ORIGINAL**

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	C _{max} (ng/ml)	T _{max} (hr)	k _{el} (hr ⁻¹)	T _{1/2} (hr)	AUC _{last} (ng.hr/ml)	AUC _{0-∞} (ng.hr/ml)	Cl _i (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	C _{max} (ng/ml)	T _{max} (hr)	k _{el} (hr ⁻¹)	T _{1/2} (hr)	AUC _{last} (ng.hr/ml)	AUC _{0-∞} (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-∞), C_{MAX}, F, T_{MAX}, K_{EL}, CLEARANCE AND VD_{SS})

Pharmacokinetic Parameter	Comparison	Adjusted Geometric Means		Ratio	95% Confidence Limits
AUC(0-∞) (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%)
C _{max} (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%)
T _{max} (hr)	Adjusted Means		Difference		
	Oral + Juice vs Oral + Placebo	7.6			
K _{el} (/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)
Cl _i (ml/min/kg)	IV + Juice vs IV + Placebo	6.8	vs 6.9	-0.2	(-1.1, 0.8)
Vd _{ss} (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 Oral Doses of 10 mg to Subjects Consuming Either Grapefruit Juice or Placebo (water)

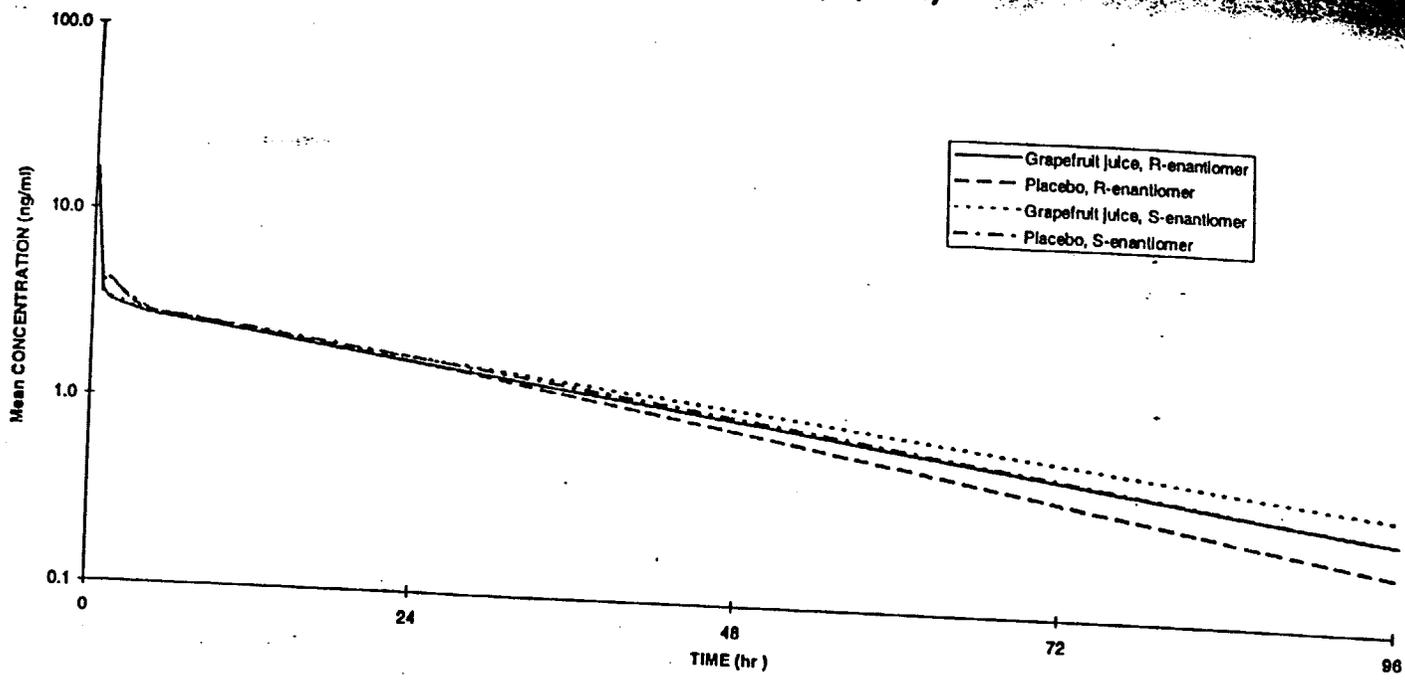


Figure 6. Mean Plasma Concentrations of R- and S-Amlodipine Following Oral Doses of 10 mg to Subjects Consuming Either Grapefruit Juice or Placebo (water)

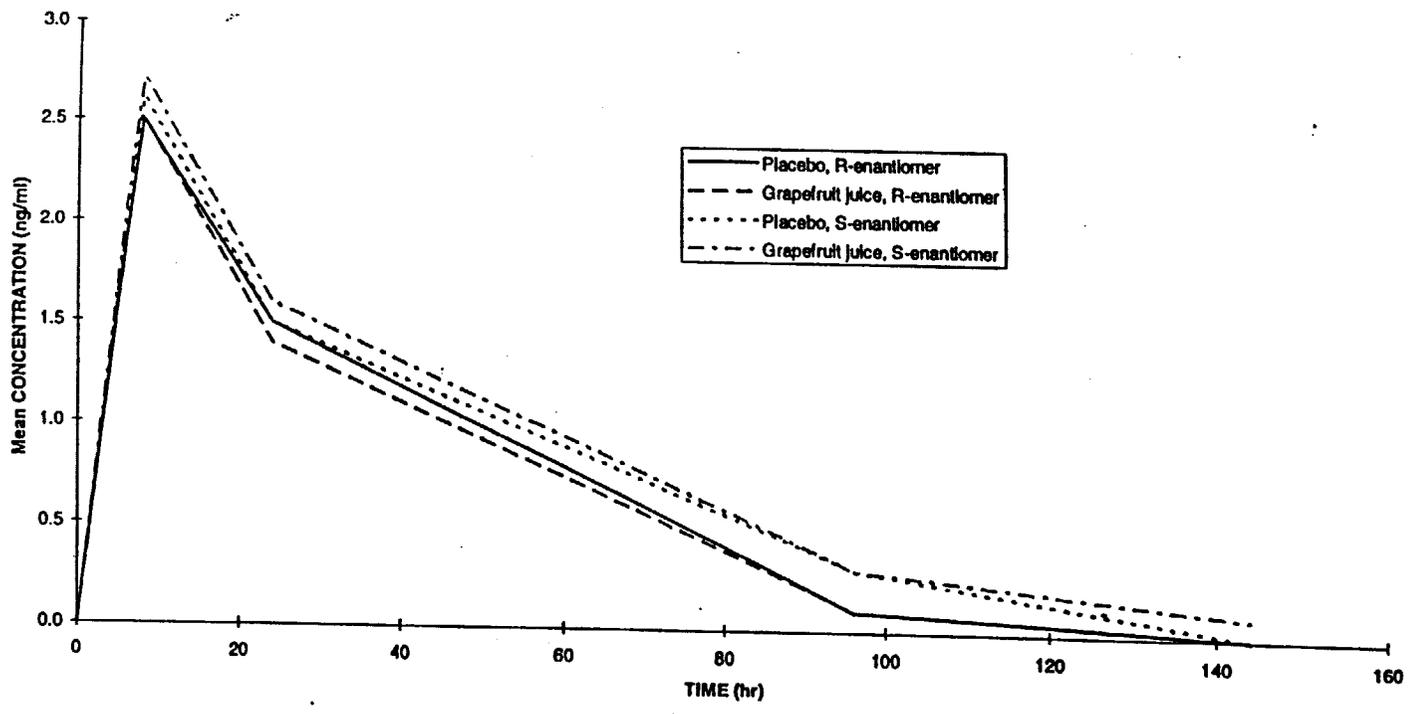


TABLE 5.3.1
AMLODIPINE PROTOCOL 053-017
SUMMARY OF STATISTICAL ANALYSES OF AMLODIPINE ENANTIOMER PARAMETERS - (SUBJECTS WITH FULL COMPLEMENT OF DATA)
IV ADMINISTRATION

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%)
C_{max} (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), C_{max}, 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), C_{max}, 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.

Study 148-225: A double-blind, placebo controlled, two way crossover study to investigate the effects of a single dose of sildenafil (100 mg) on blood pressure in subjects with essential hypertension being treated with amlodipine.

NDA 20-895
Sildenafil for male impotence

A30. Study 148-225: A double-blind, placebo controlled, two way crossover study to investigate the effects of a single dose of sildenafil (100 mg) on blood pressure in subjects with essential hypertension being treated with amlodipine.

- A30.1. Source documents** Study protocol NDA 20-895, vol 1.70; study report: NDA vol 1.70; electronic document: 47053931.pdf.
- A30.2. Investigators** Single-center study with 1 investigator in the United Kingdom.
- A30.3. Study dates** 7 August 1996 to 24 January 1997.
- A30.4. Study design** This study description was based upon the final study report, dated 29 July 1997.

A total of 16 subjects with uncomplicated hypertension treated with a stable dose of amlodipine only, age 18 to 75, were to be recruited.

On each of two clinic days separated by 7 days, subjects received a single oral dose of placebo or sildenafil 100 mg after overnight fast and 2 hours after the usual amlodipine dose. Vital signs and blood samples for assay of plasma levels of amlodipine were taken over the succeeding 8 hours.

Routine safety data were recorded.

A30.5. Results

A30.5.1. Conduct Sixteen subjects were randomized and completed study. There were minor protocol deviations, but no subject was excluded from analyses.

A30.5.2. Pharmacokinetics Pharmacokinetic parameters for amlodipine, AUC and C_{max} , were unaffected by sildenafil (with 95% confidence limits of about $\pm 20\%$). T_{max} for amlodipine did not appear to have been affected either, but the confidence limits there are much wider.

A30.5.3. Pharmacodynamics The two treatment periods had comparable vital signs at baseline. Effects on vital signs are summarized in Table 116 below. By the sponsor's analyses, most of the treatment group differences were nominally highly statistically significant.

Table 116. Effects on vital signs (Study 148-225).

		Systolic		Diastolic		Heart rate	
		Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
Max Δ (\pm SD)	Supine	-8.7 \pm 5.4	-17.0 \pm 9.7	-2.1 \pm 5.4	-7.9 \pm 5.2	-0.7 \pm 5.1	1.2 \pm 4.7
AUC (mmHg.h)		-6.1	-30.0	7.1	-5.5	-19.9	-18.8
Max Δ (\pm SD)	Standing	-9.6 \pm 7.7	-20.1 \pm 13.3	-3.0 \pm 4.6	-11.6 \pm 11.2	-3.7 \pm 4.1	3.7 \pm 6.8
AUC (mmHg.h)		-11.2	-35.1	6.8	-16.0	-28.4	-14.5

A30.5.4. Safety There were no serious or treatment-related severe adverse reactions. Adverse events overall were more common on sildenafil, headache, diarrhea, and penile erections all occurring only on sildenafil. There was one case of postural hypotension (BP fall from 136/76 mmHg supine to 68/43 mmHg standing), but a concomitant fall in pulse suggests this was vaso-vagal in nature.

A30.6. Summary Placebo-subtracted effects on supine and standing blood pressure averaged -8/-6 mmHg and -11/-9 mmHg, respectively. Little change in heart rate accompanied changes in blood pressure, but that may have been related to the background antihypertensive agent used. Blood pressure effects had onset within half an hour and persisted for several hours. Although substantial, subjects were not symptomatic, at least under the controlled clinical conditions.

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commercial

information

Annotated Package Insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19787/S17

ADMINISTRATIVE DOCUMENTS

RHPM Package Overview -- Approval

Applications: NDA 19-787/S-017
NDA 19-787/S-020
Norvasc (amlodipine besylate) Tablets

Applicant: Pfizer

Date of Supplements: November 3, 1998 (S-017)
July 2, 1999 (S-020)

Background

NDA 19-787/S-017 is a geriatric labeling supplement (see labeling review for details of labeling changes). An approvable letter was issued for this supplement on January 12, 2000 in which the firm was asked to submit final printed labeling.

NDA 19-020/S-020 is an SE8 efficacy supplement (labeling supplement with clinical data) that provides for a new **PRECAUTIONS: Drug Interactions** subsection (see labeling review for details of changes). An approvable letter was issued on April 5, 2000 in which the firm was asked to submit final printed labeling.

Pfizer submitted final printed labeling in a submission dated May 25, 2000, received May 26, 2000, in which they combined the changes from both supplements into on submission (see labeling review).

There are no outstanding issues.



David Roeder
Regulatory Health Project Manager

dr/6-28-00

cc: NDA 19-787
HFD-110
HFD-110/DRoeder/SMatthews

RHPM review of Final Printed Labeling

Application: NDA 19-787/S-017
NDA 19-787/S-020
Norvasc (amlodipine besylate) Tablets

Applicant: Pfizer

Submission Date: May 25, 2000

Receipt Date: May 26, 2000

Background

NDA 19-787-S-017 is a geriatric labeling supplement that provides for labeling revised under **PRECAUTIONS** to include a **Geriatric Use** subsection. An approvable letter was issued for this supplement on January 12, 2000, in which the firm was asked to revise the text of this subsection to read as follows:

Clinical studies of NORVASC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**).

NDA 19-787/S-020 provides for labeling revised under **PRECAUTIONS: Drug Interactions**. An approvable letter was issued to this application on April 5, 2000, in which the firm was asked to submit final printed labeling with text of this section reading as follows:

Drug Interactions: *In vitro* data in human plasma indicate that Norvasc has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Special Studies: Effect of other agents on Norvasc.

CIMETIDINE: Co-administration of Norvasc with cimetidine did not alter the pharmacokinetics of Norvasc.

GRAPEFRUIT JUICE: Co-administration of 240 mls of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy male volunteers had no significant effect on the pharmacokinetics of amlodipine.

MAALOX (antacid): Co-administration of the antacid Maalox with a single dose of Norvasc had no effect on the pharmacokinetics of Norvasc.

SILDENAFIL: A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Norvasc. When Norvasc and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of Norvasc on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of Norvasc with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of Norvasc with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of Norvasc had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of Norvasc with warfarin did not change the warfarin prothrombin response time.

In clinical trials, Norvasc has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Pfizer submitted final printed labeling for both supplements in a submission dated May 25, 2000 (received May 26, 2000).

Review

I have reviewed the final printed labeling and I found it to be identical to the approvable draft labeling with the following exception:

Under **PRECAUTIONS: Drug Interactions/Grapefruit Juice**, the applicant omitted the word "male" in reference to the volunteers.

I discussed this issue with the biopharmaceutics/clinical pharmacology reviewer, Dr. Nguyen and team leader, Dr. Marroum, and they agreed that the labeling could be approved with this deletion.

An approval letter will be drafted for Dr. Lipicky's signature.


David Roeder
Regulatory Health Project Manager

APR 5 2000

RHPM review of Draft Labeling

Application: NDA 19-787/S-020
Norvasc (amlodipine besylate) Tablets

Applicant: Pfizer

Type of Supplement: SE8, Labeling supplement with clinical data

Date of Supplement: July 1, 1999

Receipt Date: July 2, 1999

Review

NDA 19-787/S-020 provides for draft labeling revised under **PRECAUTIONS: Drug Interactions**. The entire text of this section has been replaced with the following text:

Drug Interactions: *In vitro* data in human plasma indicate that Norvasc has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Special Studies: Effect of other agents on Norvasc.

CIMETIDINE: Co-administration of Norvasc with cimetidine did not alter the pharmacokinetics of Norvasc.

GRAPEFRUIT JUICE: Co-administration of 240 mls of grapefruit juice with a 10 mg oral dose of Norvasc or a 10 mg IV infusion of amlodipine had no effect on the pharmacokinetics of Norvasc.

MAALOX (antacid): Co-administration of the antacid Maalox with a single dose of Norvasc had no effect on the pharmacokinetics of Norvasc.

SILDENAFIL: A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Norvasc. When Norvasc and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of Norvasc on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of Norvasc with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of Norvasc with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of Norvasc had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of Norvasc with warfarin did not change the warfarin prothrombin response time.

In clinical trials, Norvasc has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

The biopharmaceutics/clinical pharmacology reviewer has recommended the following revision of the firm's proposal:

Please change the text regarding the interaction of amlodipine with grapefruit juice to read as follows:

GRAPEFRUIT JUICE: Co-administration of 240 mls of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy male volunteers had no significant effect on the pharmacokinetics of amlodipine.

The Medical Officer found the proposed labeling to be acceptable.

An approvable letter will be drafted for Dr. Lipicky's signature.


David Roeder
Regulatory Health Project Manager

dr/3-24-00

cc: NDA 19-787
HFD-110
HFD-110/DRoeder/SMatthews