NDA 19-787/S-017
S-020

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,

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