DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-787/S-037

Pfizer Inc.
Attention: Mr. Robert Clark
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug application dated January 14, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norvasc (amlodipine besylate) 2.5, 5, and 10 mg Tablets.

This "Changes Being Effected" supplemental new drug application provides for electronic final printed labeling with revisions to the NORVASC label to ensure consistency with the labeling text for CADUET (amlodipine besylate and atorvastatin calcium). Revisions have been made to the **DESCRIPTION**, **CLINICAL PHARMACOLOGY**, **PRECAUTIONS**, and **OVERDOSAGE** sections as follows:

1. Under the **DESCRIPTION** section, the chemical description in the second paragraph was changed to:

   Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.

2. Under **CLINICAL PHARMACOLOGY/Mechanism of Action**, the trade name, NORVASC, was substituted with the established name, amlodipine, throughout the first, second and third paragraphs to read as follows:

   Amlodipine 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 amlodipine 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. Amlodipine 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 amlodipine. Within the physiologic pH range, amlodipine 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.

Amlodipine 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 amlodipine relieves angina have not been fully delineated, but are thought to include the following:

3. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism,** the trade name, NORVASC, was substituted with amlodipine in the first and second paragraphs to read as follows:

   Amlodipine 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 amlodipine are reached after 7 to 8 days of consecutive daily dosing.

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

4. Under **CLINICAL PHARMACOLOGY/Pediatric Patients**, the first sentence was changed to:

   Sixty-two hypertensive patients aged 6 to 17 years received doses of NORVASC between 1.25 mg and 20 mg.

5. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics/Hemodynamics**, the word "oral" was placed in front of the word "administration" in the third sentence to read as follows:

   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 oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

6. The new heading "**CLINICAL STUDIES"** was added before the **Effects in Hypertension** subsection.

7. The **Studies in Patients with Congestive Heart Failure** subsection, which was originally located in the **CLINICAL PHARMACOLOGY** section before **Electrophysiologic Effects** subsection, was moved and placed as the last subsection in the **CLINICAL STUDIES** section.

8. Under **CLINICAL STUDIES/ Studies in Patients with Congestive Heart Failure,** the abbreviation LVEF in the second sentence was replaced with the words left ventricular ejection fraction.

9. Under **PRECAUTIONS**/**General**, the paragraph has been revised to read as follows:

   Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution as with any other peripheral

vasodilator, should be exercised when administering NORVASC, particularly in patients with severe aortic stenosis.

10. Under **PRECAUTIONS/Drug Interactions**, the sentence has been revised to read as follows:

    In vitro data indicate that NORVASC has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

11. Under **PRECAUTIONS**, the words "**Special Studies**" have been deleted before the ***Effect of other agents on Norvasc*** subsection.

12. Under **PRECAUTIONS**, the subsections, ***Effect of other agents on Norvasc*** and ***Effect of NORVASC on other agents*** have been italicized**.**

13. Under **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** section, the paragraphs have been revised to read as follows:

    Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day*). For the rat, the highest dose was, on a mg/m^2 basis, about twice the maximum recommended human dose*.

    Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

    There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis).

14. Under **PRECAUTIONS/Pregnancy Category C**, the paragraph was changed to read as follows:

    No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m^2 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 receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate 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.

15. Under the third table in the **ADVERSE REACTIONS** section, the abbreviation ADR was

replaced with the words, Adverse Event.

16. Under **OVERDOSAGE**, the first paragraph has been revised to read as follows:

    Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

17. Under **OVERDOSAGE**, the following sentence has been deleted from the second paragraph:

    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.

    The second paragraph now reads as follows:

    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 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.

We have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the electronic final printed labeling (package insert included in your submission of January 18, 2005).

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Package Insert)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge

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