DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19-787/S-045 **SUPPLEMENT APPROVAL**

Pfizer Inc.
Attention: Tricia Douglas
Manager, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Douglas:

Please refer to your supplemental new drug application dated February 24, 2009, received February 24, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Norvasc (amlodipine besylate) 2.5 mg, 5 mg, and 10 mg Tablets.

We acknowledge receipt of your submissions dated August 13 and 24, September 1, December 8, 2009 and January 26, 2010.

This supplemental new drug application provides for conversion to the new Physicians Labeling Rule Format. The following changes have been made:

1. The labeling has been converted to the Physician Labeling Rule format.

2. In **DOSAGE AND ADMINISTRATION/Adults**, the word "patients" has replaced the word "individuals" in the first sentence of the second paragraph.

3. In **DOSAGE AND ADMINISTRATION/Adults**, in the first sentence of the third paragraph the passive voice was converted to active voice. The sentence now reads:

   Adjust dosage according to each patient's need.

4. In **DOSAGE AND ADMINISTRATION**, the following text was deleted:

   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.

5. In **WARNINGS AND PRECAUTIONS/Hypotension**, the first paragraph has been changed from:

   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.

To:

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension in unlikely.

6. In **WARNINGS AND PRECAUTIONS/Increased Angina or Myocardial Infarction**, the first paragraph has been changed from:

   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.

   To:

   Worsening of angina and acute myocardial infarction can develop after starting or increasing the dose of NORVASC, particularly in patients with severe obstructive coronary artery disease.

7. In **WARNINGS AND PRECAUTIONS**, the paragraph titled **Use in Patients with Congestive Heart Failure** has been deleted.

8. In **WARNINGS AND PRECAUTIONS/Patients With Hepatic Failure**, the first paragraph has been changed from:

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

   To:

   Because NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, titrate slowly when administering NORVASC to patients with severe hepatic impairment.

9. In **ADVERSE REACTIONS/Clinical Trial Experience**, the following has been added as the first paragraph:

   Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared

to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

10. In **ADVERSE REACTIONS/Postmarketing Experience**, the following has been added as the first paragraph:

    Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

11. In **DRUG INTERACTIONS**, the title of **7.4** has been revised from:

    MAALOX

    To:

    Magnesium and Aluminum Hydroxide Antacid

12. In **DRUG INTERACTIONS**/Sildenafil, the word "Viagra®" has been deleted. The paragraph now reads:

    A single 100 mg dose of sildenafil 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.

13. In **DRUG INTERACTIONS**/Warfarin, the following text has been deleted:

    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.

14. In **OVERDOSAGE**, the section was changed from:

    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/m2 basis) 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 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.

To:

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.

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.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

15. In **NONCLINICAL TOXICOLOGY/Carcinogenesis, Mutagenesis, Impairment of Fertility**, "[3] based on patient weight of 50 kg" has been added as a footnote.

16. In **CLINICAL STUDIES/Effects in Hypertension/Pediatric Patients**, the first paragraph has been revised from:

    Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to NORVASC 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5-mg dose. Adverse events were similar to those seen in adults.

    To:

    Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to NORVASC 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults.

17. In **CLINICAL STUDIES**, the title of **14.5** has been revised from:

    Studies in Patients with Congestive Heart Failure

    To:

    Studies in Patients with Heart Failure

18. In the Patient Package Insert/**What are the possible side effects of NORVASC?**, the word “taking” has been added to the first sentence of the second paragraph. The paragraph now reads:

    It is rare, but when you first start taking NORVASC or increase your dose, you may have a heart attack or your angina may get worse. If that happens, call your doctor right away or go directly to a hospital emergency room.

19. In the Patient Package Insert, the telephone number for product information was updated.

20. The revision date and version number were updated on the label and the Patient Package Insert.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 019787/S-045.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Agreed-upon Labeling Text
Agreed-upon Text for Patient Package Insert

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19787	SUPPL-45	PFIZER INC	NORVASC

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

/s/

NORMAN L STOCKBRIDGE
02/17/2010