DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019787/S-053
NDA 019787/S-054

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 Applications (sNDAs) dated February 9 (S-053) and May 15, 2012 (S-054), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Norvasc (amlodipine besylate) 2.5 mg, 5.0 mg and 10 mg Tablets.

These "Prior Approval" supplemental new drug applications provide for revisions pertaining to the March 2011 Guidance for Industry "*Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims*", revisions to update the labeling with approved language in the amlodipine portions of the Caduet label and the addition of Drug Interaction language related to cyclosporine. The following content changes were made, other editorial changes were made throughout the label;

In **HIGHLIGHTS**, the following were added or ~~deleted~~;

Under INDICATIONS AND USAGE;

- Hypertension (1.1)
  - NORVASC is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Under WARNINGS AND PRECAUTIONS;

- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, ~~because of the gradual onset of action,~~ acute hypotension is unlikely. (5.1)
- Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of NORVASC, particularly in patients with severe obstructive coronary artery disease. (5.2)
- Titrate slowly ~~when administering calcium channel blockers to~~ in patients with severe hepatic impairment. (5.3)

Under ADVERSE REACTIONS;

Most common adverse reaction to amlodipine is ~~are headache and~~ edema which occurred in a dose related manner. Other adverse experiences not dose related but reported with an incidence >1.0% are ~~headache~~, fatigue, nausea, abdominal pain, and somnolence. (6)

Under DRUG INTERACTIONS;

- ~~If simvastatin is co-administered with amlodipine, d~~Do not exceed doses greater than 20 mg daily of simvastatin. (7.7)

Under USE IN SPECIFIC POPULATIONS;

- Pregnancy: Use only if the potential benefit justifies the ~~potential~~ risk. (8.1)
- Nursing: Discontinue when administering NORVASC. (8.3)
- Pediatric: Effect on patients less than 6 years old is not known. (8.4)
- Geriatric: Start dosing at the low end of the dose range, ~~due to the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. (8.5)~~

In **FULL PRESCRIBING INFORMATION**, the following were added or ~~deleted~~;

Under INDICATIONS AND USAGE;

NORVASC® is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including NORVASC.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction

from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

NORVASC may be used alone or in combination with other antihypertensive agents.

Under DOSAGE AND ADMINISTRATION;

2.1 Adults

The usual initial antihypertensive oral dose of NORVASC is 5 mg once daily, and the ~~with a~~ maximum dose ~~of~~ is 10 mg once daily.

Small, fragile, or elderly patients, 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.

Adjust dosage according to ~~each patient's need~~ blood pressure goals. In general, ~~titration should proceed over~~ wait 7 to 14 days ~~so that the physician can fully assess the patient's response to each dose level~~ between titration steps. Titrate ~~ion may proceed~~ more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: 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.

Coronary artery disease: The recommended dose range for patients with coronary artery disease is 5–10 mg once daily. In clinical studies, the majority of patients required 10 mg *[see Clinical Studies (14.4)]*.

Under WARNINGS AND PRECAUTIONS;

~~**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.~~

Under ADVERSE REACTIONS;

Clinical Trials Experience

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.

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) at doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC ~~due to~~ because of adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most commonly reported side effects more frequent than placebo are reflected in the table below ~~headache and edema~~. The incidence (%) of side effects that occurred in a dose related manner are as follows:

~~Adverse Event~~	Amlodipine			Placebo
	2.5 mg	5~~.0~~ mg	10~~.0~~ mg	
	N=275	N=296	N=268	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~~ reactions that were not clearly dose related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

~~**Placebo-Controlled Studies**~~	NORVASC (%)	Placebo (%)
	(N=1730)	(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:

~~**Adverse Event**~~	NORVASC		Placebo	
	Male=%	Female=%	Male=%	Female=%
	(N=1218)	(N=512)	(N=914)	(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,~~[1] dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia,[1] back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps,[1] myalgia.

Psychiatric: sexual dysfunction (male[1] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea,[1] epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus,[1] rash,[1] rash erythematous, rash maculopapular.

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.

[1] 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.
~~The following events occurred in <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.

In the CAMELOT and PREVENT studies *[see Clinical Studies (14.4)]*, the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema.

Under DRUG INTERACTIONS;

7.13 Cyclosporine

A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine.

Under USE IN SPECIFIC POPULATIONS;

8.1 Pregnancy

Pregnancy Category C

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.

8.4 Pediatric Use

NORVASC (2.5 to 5 mg daily) is effective in lowering blood pressure in patients 6 to 17 years *[see Clinical Studies (14.1)]*. Effect of NORVASC on blood pressure in patients less than 6 years of age is not known.

We have completed our review of this supplemental application. 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, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

MARY R SOUTHWORTH
01/07/2013