DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021990/S-014

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy Price
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your Supplemental New Drug Application (sNDA) dated April 6, 2011, received April 6, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exforge (amlodipine and valsartan) Tablets, 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg.

We acknowledge receipt of your amendments dated June 15 and November 23, 2011.

This "Prior Approval" supplemental new drug application provides for changes in accordance with the Guidance for Industry, *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims.* A **CONTRAINDICATIONS** section has also been added to explicitly state "None".

These changes have been made as follows:

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

1. The section RECENT MAJOR CHANGES was added as follows:

   ----------RECENT MAJOR CHANGES----------

Indications and Usage: Benefits of lowering blood pressure (1)	12/2011
Contraindications (4)	12/2011

2. Under **INDICATIONS AND USAGE**, the following changes were made (additions are shown as underlined text):

   Exforge is the combination tablet of amlodipine, a dihydropyridine calcium channel blocker (DHP CCB), and valsartan, an angiotensin II receptor blocker (ARB). Exforge is indicated for the treatment of hypertension, to lower blood pressure:
   - In patients not adequately controlled on monotherapy (1)
   - As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals (1). Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

3. A new section "CONTRAINDICATIONS" was added as follows:

----------CONTRAINDICATIONS----------
None

In **FULL PRESCRIBING INFORMATION: CONTENTS***

4. A new section heading "**4 CONTRAINDICATIONS**" was added.

In **FULL PRESCRIBING INFORMATION**

5. Under 1 INDICATIONS AND USAGE, the following changes were made (additions are shown as underlined text):

1.1 Hypertension

Exforge (amlodipine and valsartan) 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 amlodipine and the ARB class to which valsartan principally belongs. There are no controlled trials demonstrating risk reduction with Exforge.

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.

6. A new section "4 CONTRAINDICATIONS" has been added to explicitly state that there are no contraindications as follows:

   4 CONTRAINDICATIONS
   None

7. Under 14 CLINICAL STUDIES, the following was added at the end of this section:

   There are no trials of the Exforge combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but the amlodipine component and several ARBs, which are the same pharmacological class as the valsartan component, have demonstrated such benefits.

8. The revision date and label version number have been updated.

We have completed our review of this supplemental application, as amended. 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, text for the patient 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 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 contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

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:
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/

NORMAN L STOCKBRIDGE
12/07/2011