DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020818/S-046 and S-049

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 August 12, 2010, received August 12, 2010 for S-046 and dated April 7, 2011, received April 7, 2011 for S-049, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Diovan HCT (valsartan/hydrochlorothiazide) Tablets, 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, and 320/25 mg.

We acknowledge receipt of your amendment dated October 22, 2010 for S-046.

S-046

This Changes Being Effected labeling supplement provides for editorial corrections and clinical pharmacology changes as per our Approval Letter for S-043 dated April 21, 2010. The addition of large count bottles under **16 HOW SUPPLIED/STORAGE AND HANDLING** has also been included.

The following changes have been made:

1. Under Section **7 DRUG INTERACTIONS**, **Valsartan**, the following paragraph was changed from:

> *CYP 450 Interactions:* The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.
>
> To:
>
> *CYP 450 Interactions: In vitro* metabolism studies indicate that CYP 450 mediated drug interactions between valsartan and co-administered drugs are unlikely because of the low extent of metabolism *[see Clinical Pharmacology (12.3)]*.
>
> *Transporters:* The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

2. Under Section **12.3 Pharmacokinetics**, **Metabolism**, **Valsartan**, the second sentence was changed from:

   The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

   To:

   In vitro metabolism studies involving recombinant CYP 450 enzymes indicated that the CYP 2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP 450 isozymes at clinically relevant concentrations. CYP 450 mediated drug interaction between valsartan and co-administered drugs are unlikely because of the low extent of metabolism.

3. Under **16 HOW SUPPLIED/STORAGE AND HANDLING** the addition of large count bottles and assigned NDC numbers have been added.

4. The listing of "16. HOW SUPPLIED/STORAGE AND HANDLING" was re-added under the **FULL PRESCRIBING INFORMATION: CONTENTS*** section.

5. For all references throughout the FPI, the brackets were italicized and the letter "S" in the word "See" was changed to lowercase type.

6. Under **2.1 General Considerations**, *Hepatic impairment*, the reference at the end of this section was changed from:

   [*See Impaired Hepatic Function (5.3)*]

   To

   [see Warnings and Precautions (5.3)]

7. Under Section **8.1 Pregnancy**, the number in the reference parentheses at the end of this section was changed from 13.2 to 13 so that the reference reads *"[see Nonclinical Toxicology (13)]*."

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

S-049

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.* Class labeling language has also been added under **7 DRUG INTERACTIONS** regarding Non-Steroidal Anti-Inflammatory Agents (NSAIDs).

The following changes have been made (additions are shown as underlined text):

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

9. The listing "Indications and Usage: Benefits of lowering blood pressure (1) 12/2011" was added to RECENT MAJOR CHANGES as follows:

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

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

Warnings and Precautions: Acute Angle-Closure Glaucoma (5.9) 2/2011

10. Under **INDICATIONS AND USAGE**, the following changes were made:

Diovan HCT is indicated for the treatment of hypertension, to lower blood pressure:
- In patients not adequately controlled with 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.

In **FULL PRESCRIBING INFORMATION**

11. Under **1 INDICATIONS AND USAGE**, the following was added:

Diovan HCT (valsartan and hydrochlorothiazide, USP) 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 hydrochlorothiazide and the ARB class to which valsartan principally belongs. There are no controlled trials demonstrating risk reduction with Diovan HCT.

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.

12. Under **7 DRUG INTERACTIONS**, the following was added at the end of the **Valsartan** subsection:

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

13. Under **14 CLINICAL STUDIES**, the following was added at the end of the **14.1 Hypertension, Valsartan-Hydrochlorothiazide** subsection:

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

In **Patient Information**

14. Under **"What should I tell my doctor before taking DIOVAN HCT?"**, in the 9th bullet under "**Tell your doctor about all the medicines you take**", the phrase "like ibuprofen or naproxen" has been added so that the bullet reads as follows:

- aspirin or other medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), like ibuprofen or naproxen

We have completed our review of these supplemental applications, as amended, and they are 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
12/12/2011