DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021283/S-037
NDA 020818/S-054

SUPPLEMENT APPROVAL

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

Dear Ms Price:
This letter supersedes the previous action letter dated July 26, 2012, for these supplements. The original letter contained several errors as follows:

- The text *and potassium* was missing from #4 for NDA 021283
- The text *Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine* was inadvertently shown as underlined text in #11 for NDA 021283
- The text *Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance)* was inadvertently shown as strikethrough text for NDA 021283

The effective date of the action will remain July 26, 2012, the date of the original action letter.

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received March 9, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Diovan (valsartan) 40 mg, 80 mg, 160 mg, 320 mg (NDA 021283) Tablets, and Diovan HCT (valsartan/hydrochlorothiazide) 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, and 320/25 mg Tablets (020818).

We acknowledge receipt of you amendment dated July 2, 2012 for NDA 021283. We also acknowledge receipt of your amendments dated June 29, and July 3, 2012 for NDA 020818.

These "Prior Approval" supplemental new drug applications provide for labeling revised as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough text~~):

For NDA 021283:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES** the following text was added:

Contraindications: Known hypersensitivity (4) 7/2012

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the following text was ~~deleted~~:

> ~~No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment. Diovan may be administered with or without food. In heart failure patients, consideration should be given to reducing the dose of concomitant diuretics. Following myocardial infarction, consideration should be given to a dosage reduction if symptomatic hypotension or renal dysfunction occurs.~~

3. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following text was added/~~deleted~~:

> ~~None~~Known hypersensitivity to any component (4)

4. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was added/~~deleted~~:

> ~~• Avoid fetal or neonatal exposure (5.1)~~
> • Observe for signs and symptoms of hypotension (5.2)
> • ~~Use with caution in patients with impaired hepatic (5.3) or renal (5.4) function~~ Monitor renal function and potassium in susceptible patients (5.3)

5. In **HIGHLIGHTS/USE IN SPECIFIC POPULATIONS**, the following text was ~~deleted~~:

> ~~**Geriatrics**: No overall difference in efficacy or safety vs. younger patients, but greater sensitivity of some older individuals cannot be ruled out (8.5)~~

6. Under **CONTRAINDICATIONS**, the following text was added/~~deleted~~:

> ~~None~~ Do not use in patients with known hypersensitivity to any component.

7. Under **WARNINGS AND PRECAUTIONS,** the following text was added/~~deleted~~:

> ~~**5.3 Impaired Hepatic Function**~~
>
> ~~As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan to these patients.~~
>
> **5.4 Impaired Renal Function**
>
> ~~In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. As a consequence of inhibiting the renin-angiotensin-aldosterone~~

~~system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan. Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage education and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.~~ Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g. patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Diovan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Diovan.

5.4 Hyperkalemia

Some patients with heart failure have developed increases in potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of Diovan may be required *[see Adverse Reactions (6.1)]*.

8. Under **ADVERSE REACTIONS/Heart Failure**, the following text was added/~~deleted~~ from the second paragraph:

The table shows adverse reactions in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers. About 93% of patients received concomitant ~~or~~ ACE inhibitors. Discontinuations occurred in 0.5% of valsartan-treated patients and 0.1% of placebo patients for each of the following: elevations in creatinine and elevations in potassium.

9. Under **ADVERSE REACTIONS/Post-Myocardial Infarction,** the following text was added:

Discontinuations due to renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients.

10. Under **ADVERSE REACTIONS/Post-Marketing Experience**, the following text was added:

Hypersensitivity: There are rare reports of angioedema. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Diovan should not be re-administered to patients who have had angioedema.

Renal: Impaired renal function, renal failure

11. Under **DRUG INTERACTIONS**, the following text was added/~~deleted~~:

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.~~*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)].*

Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

12. Under **USE IN SPECIFIC POPULATIONS**, the following text was added:

8.6 Renal Impairment

Safety and effectiveness of Diovan in patients with severe renal impairment (CrCl ≤ 30 mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60-90 mL/min) or moderate (CrCl 30-60) renal impairment.

8.7 Hepatic Impairment

No dose adjustment is necessary for patients with mild-to-moderate liver disease. No dosing recommendations can be provided for patients with severe liver disease.

13. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/~~deleted~~:

Metabolism and Elimination: Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. ~~The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.~~ Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance). *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.

14. Under **PATIENT COUNSELING INFORMATION/Tell your doctor about all your medical conditions including whether you:**, the following text was added:

    - have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue and/or throat, and may cause difficulty breathing.

    Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you take:
    - other medicines for high blood pressure or a heart problem
    - water pills (also called "diuretics")
    - potassium supplements. Your doctor may check the amount of potassium in your blood periodically
    - a salt substitute. Your doctor may check the amount of potassium in your blood periodically
    - Nonsteroidal anti-inflammatory drugs (like ibuprofen or naproxen)
    - certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporin) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.

15. The revision date and version number were updated.

There are no other changes from the last approved package insert.

For NDA 020818:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES** the following text was added:

    Warnings and Precautions: Serum Electrolyte Abnormalities (5.7) 07/2012

2. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following text was added:

    Anuria; Hypersensitivity to any sulfonamide-derived drugs or any component (4)

3. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the following text was added to the third bullet:

    - Monitor renal function and potassium in susceptible patients (5.3)

4. Under **WARNINGS AND PRECAUTIONS/Potassium Abnormalities,** the following text was added/~~deleted~~:

    Valsartan: Some patients with heart failure have developed increases in potassium with Diovan therapy. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or

discontinuation of the diuretic and/or Diovan may be required ~~In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, discontinuations occurred in 0.5% of valsartan-treated patients and 0.1% of placebo patients for each of the following: elevations in creatinine and elevations in potassium. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function~~ *[see Adverse Reactions (6.1)]*.

5. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following text was added:

Hypersensitivity: There are rare reports of angioedema. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Diovan HCT should not be re-administered to patients who have had angioedema.

6. Under **DRUG INTERACTIONS**, the following text was added:

Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

7. In the **FDA-Approved Patient Labeling**, under **Tell your doctor about all your medical conditions including if you:,** a tenth bullet was added:

- have ever had a reaction called angioedema to another blood pressure medication. Angioedema causes swelling of the face, lips, tongue, throat, and may cause difficulty breathing.

8. In the **FDA-Approved Patient Labeling**, under **Tell you doctor about all the medicines you take**, the third and fourth bullets were changed:

- potassium supplements. Your doctor may check the amount of potassium in your blood periodically.
- a salt substitute. Your doctor may check the amount of potassium in your blood periodically. ~~containing potassium~~

9. In the **FDA-Approved Patient Labeling**, under **Tell you doctor about all the medicines you take**, a thirteenth bullet was added:

- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporin) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.

10. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of these supplemental applications, 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), 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include

prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 for Safety
(301) 796-3975

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:
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
07/26/2012