DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020665/S-033

SUPPLEMENT APPROVAL

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

Dear Ms. Price:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 10, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Diovan (valsartan 80 mg and 160 mg Capsules.

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

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

~~Boxed Warning: Fetal Toxicity~~	~~01/2012~~
~~Indications and Usage: Benefits of lowering blood pressure (1)~~	~~12/2012~~
~~Dosage and Administration:~~	
~~Pediatric Hypertension 6-16 years of age (2.2)~~	~~02/2012~~
~~Contraindications: Known Hypersensitivity (4)~~	~~07/2012~~
Contraindications: Dual RAS Blockade in Diabetics (4)	10/2012
~~Warnings and Precautions: Fetal Toxicity (5.1)~~	~~01/2012~~
Drug Interactions:	
Dual Blockade of the Renin-Angiotensin System (7)	10/2012

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

Do not coadminister aliskiren with Diovan in patients with diabetes (4)

3. In **HIGHLIGHTS/DRUG INTERACTIONS**, a bullet was added:

- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7)

4. Under **DOSAGE AND ADMINISTRATION/Pediatric Hypertension 6-16 year of age,** the following text was added/deleted:

> For children who can swallow capsules, the usual recommended starting dose is 1.3 mg/kg once daily (up to 40 mg total). (Doses below 80 mg are available only in the tablet form.) The dosage should be adjusted according to blood pressure response. Doses higher than 2.7 mg/kg (up to 160 mg) once daily have not been studied in pediatric patients 6 to 16 years old.
>
> For children who cannot swallow capsules or tablets, or children for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths of Diovan, the use of a suspension is recommended. ~~Follow t~~The suspension preparation instructions are available based on the Diovan tablet form. ~~below (see **Preparation of Suspension**) to administer valsartan as a suspension. When the suspension is replaced by a tablet, the dose of valsartan may have to be increased. The exposure to valsartan with the suspension is 1.6 times greater than with the tablet.~~
>
> ~~**Preparation of Suspension (for 160 mL of a 4 mg/mL suspension)**~~
> ~~Add 80 mL of Ora-Plus®* oral suspending vehicle to an amber glass bottle containing 8 Diovan 80 mg tablets, and shake for a minimum of 2 minutes. Allow the suspension to stand for a minimum of 1 hour. After the standing time, shake the suspension for a minimum of 1 additional minute. Add 80 mL of Ora-Sweet SF®* oral sweetening vehicle to the bottle and shake the suspension for at least 10 seconds to disperse the ingredients. The suspension is homogenous and can be stored for either up to 30 days at room temperature (below 30°C/86°F) or up to 75 days at refrigerated conditions (2-8°C/35-46°F) in the glass bottle with a child-resistant screw-cap closure. Shake the bottle well (at least 10 seconds) prior to dispensing the suspension.~~
>
> ~~*Ora-Sweet SF® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.~~

5. Under **DOSAGE AND ADMINISTRATION,** the following sentence was added as the second sentence in the first paragraph of Section 2.3 and as the fourth sentence in the first paragraph of Section 2.4:

> (Doses below 80 mg are available only in the tablet form.)

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

> Do not coadminister aliskiren with Diovan in patients with diabetes [*See Drug Interactions (7)*].

7. Under **WARNINGS AND PRECAUTIONS/Impaired Renal Function**, the following cross reference was added:

   [See Drug Interactions (7)].

8. Under **WARNINGS AND PRECAUTIONS/Fetal Toxicity**, the following text was added:

   Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Diovan as soon as possible. *[see Use in Specific Populations (8.1)]*.

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

   Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on Diovan and other agents that affect the RAS.

   Do not coadminister aliskiren with Diovan in patients with diabetes. Avoid use of aliskiren with Diovan in patients with renal impairment (GFR <60 mL/min).

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

    Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Diovan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Diovan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Diovan for hypotension, oliguria, and hyperkalemia. [*see Use in Specific Populations (8.4)]*

11. Under **USE IN SPECIFIC POPULATIONS/Pediatric Use**, the following text was added:

Neonates with a history of in utero exposure to Diovan:
If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

12. Under **DOSAGE FORMS AND STRENGTHS**, the following text was added/deleted:

~~40 mg are scored yellow ovaloid tablets with beveled edges, imprinted NVR/DO (Side 1/Side 2)~~
80 mg are light pink and light grey capsules, ~~pale red almond shaped tablets with beveled edges~~ imprinted CG/FZF
160 mg are light pink and dark grey capsules, ~~grey orange almond shaped tablets with beveled edges~~ imprinted CG/GOG
~~320 mg are dark grey violet almond shaped tablets with beveled edges, imprinted NVR/DXL~~

13. Under **DESCRIPTION**, the following text was added/deleted:

Diovan is available as ~~tablets~~ capsules for oral administration, containing ~~40 mg,~~ 80 mg or 160 mg ~~or 320 mg~~ of valsartan. The inactive ingredients of the tablets are ~~colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.~~ cellulose compounds, crospovidone, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

14. Under **HOW SUPPLIED/STORAGE AND HANDLING**, the following text was added/deleted:

Capsule	Color Light pink	Imprint	NDC	
			Bottle	Blister
80 mg	Light grey	CG FZF	0083-4000-01	0083-4000-61
160 mg	Dark grey	CG GOG	0083-4001-01	0083-4001-61

~~40 mg tablets are scored on one side and ovaloid with bevelled edges. 80 mg, 160 mg, and 320 mg tablets are unscored and almond-shaped with bevelled edges.~~

~~Tablet~~	~~Color~~	~~Deboss~~		~~NDC 0078-#### ##~~					
		~~Side 1~~	~~Side 2~~	~~Bottle of~~					~~Blister~~
				~~30~~	~~90~~	~~3500~~	~~7000~~	~~14000~~	~~Packages of 100~~
~~40 mg~~	~~Yello~~	~~NVR~~	~~DO~~	~~0423-15~~	~~–~~	~~–~~	~~–~~	~~–~~	~~0423-06~~
~~80 mg~~	~~Pale red~~	~~NVR~~	~~DV~~	~~–~~	~~0358-34~~	~~–~~	~~–~~	~~0358-33~~	~~0358-06~~
~~160 mg~~	~~Grey-orange~~	~~NVR~~	~~DX~~	~~–~~	~~0359-34~~	~~–~~	~~0359-17~~	~~–~~	~~0359-06~~
~~320 mg~~	~~Dark grey~~	~~NVR~~	~~DXL~~	~~–~~	~~0360~~	~~0360~~	~~–~~	~~–~~	~~0360-06~~

15. Under **PATIENT COUNSELING INFORMATION**, the following text was added:

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to Diovan during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

16. The word "capsule" replaces the word "tablet" in multiple places.

17. 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 this supplemental application, 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, 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 1
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
10/29/2013