DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021283/S-035

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 July 11, 2011, received July 11, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Diovan (valsartan) Tablets, 40, 80, 160, 320 mg.

We acknowledge receipt of your amendments dated January 17 and February 9, 2012.

This "Prior Approval" supplemental new drug application provides for the addition of further safety information for the use of Diovan in pediatric hypertension.

The following changes have been made (additions are shown as underlined text and deletions are shown as ~~strike-through text~~):

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

1. The **RECENT MAJOR CHANGES** section was updated as follows:

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

   Indications and Usage: Benefits of lowering blood pressure (1) 12/2011
   Dosage and Administration
   Pediatric Hypertension 6-16 years of age (2.2) 2/2012

2. Under **USE IN SPECIFIC POPULATIONS**, **Pediatrics**, the following addition was made:

   Pediatrics: Efficacy and safety data support use in 6-16 year old patients (8.4); use is not recommended in patients <6 years old (6.1, 8.4);

In **FULL PRESCRIBING INFORMATION**

3. Under **2.2 Pediatric Hypertension 6-16 years of age**, the following changes were made to the 3rd paragraph:

No data are available in pediatric patients ~~Diovan is not recommended for treatment of children below the age of 6 years or children of any age~~ either undergoing dialysis or with a glomerular filtration rate <30 mL/min/1.73 m^2~~, as no data are available~~. *[See Pediatric Use (8.4)]*

Diovan is not recommended for patients <6 years old. *[See Adverse Reactions (6.1), Clinical Trials (14.1)]*

4. In **6.1 Clinical Studies Experience**, **Pediatric Hypertension**, the following changes were made:

Diovan has been evaluated for safety in over 400 pediatric patients aged 6 to 17 years and more than 160 pediatric patients aged 6 months to 5 years. No relevant differences were identified between the adverse experience profile for pediatric patients aged 6-16 years and that previously reported for adult patients. Headache and hyperkalemia were the most common adverse events suspected to be study drug-related in older children (6 to 17 years old) and younger children (6 months to 5 years old), respectively. Hyperkalemia was mainly observed in children with underlying renal disease. Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years revealed no overall clinically relevant adverse impact after treatment with Diovan for up to one year.

Diovan is not recommended for pediatric patients under 6 years of age. In a~~the one~~ study (n=90) of pediatric patients (1-5 years), two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. These 5 events occurred in a study population in which patients frequently had significant co-morbidities. A causal relationship to Diovan has not been established. In a second study in which 75 children aged 1 to 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a one year open-label extension.

5. Under **7 DRUG INTERACTIONS**, the following changes were made to the 2nd paragraph under *Transporters*:

C~~As with other drugs that block angiotensin II or its effects, c~~oncomitant 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.

6. Under **8.4 Pediatric Use**, the following changes were made:

8.4 Pediatric Use

The antihypertensive effects of Diovan have been evaluated in two randomized, double-blind clinical studies in pediatric patients from 1-5 and 6-16 years of age *[see Clinical Studies (14.1)]*. The pharmacokinetics of Diovan have been evaluated in pediatric patients 1 to 16 years of age *[see Pharmacokinetics, Special Populations, Pediatric (12.3)]*. Diovan was generally well tolerated in children 6-16 years and the adverse experience profile was similar to that described for adults.

In children and adolescents with hypertension where underlying renal abnormalities may be more common, renal function and serum potassium should be closely monitored as clinically indicated.

Diovan is not recommended for pediatric patients under 6 years of age due to safety findings for which a relationship to treatment could not be excluded *[see Adverse Reactions, Pediatric Hypertension (6.1)]*.

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate <30 mL/min/1.73 m^2.

There is limited clinical experience with Diovan in pediatric patients with mild to moderate hepatic impairment *[See Warnings (5.3)]*.

Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (about 10% of the maximum recommended pediatric dose on a mg/m^2 basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. Since this period coincides with up to 44 weeks after conception in humans, it is not considered to point toward an increased safety concern in 6 to 16 year old children.

~~Diovan is not recommended for treatment of children with glomerular filtration rates <30 mL/min/1.73 m^2, as no data are available.~~

In **Patient Information**

7. Under "**What at the possible side effects of DIOVAN?**" under **Kidney Problems**, the following changes were made in the first two sentences:

   Kidney problems. Kidney problems may get worse if ~~in people~~you ~~that~~ already have kidney disease. Some ~~people~~ patients will have changes on blood tests for kidney function and may need a lower dose of DIOVAN.

Minor editorial changes

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

9. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION**, under **DOSAGE and ADMINISTRATION**, the reference numbers in parenthesis in the table were updated as follows:

   Pediatric Hypertension (6-16 years) (2.2~~1~~)
   Heart Failure (2.3~~2~~)
   Post-Myocardial Infarction (2.4~~3~~)

10. In the **FULL PRESCRIBING INFORMATION**, under **12.3 Pharmacokinetics**, the reference number parenthetical in the 4th sentence has been re-located to the end of the reference as follows:

    The bioavailability of the suspension (see ~~[2.2]~~ *Dosage and Administration; Pediatric Hypertension (2.2))* is 1.6 times greater than with the tablet.

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}

Mary Ross Southworth, Pharm.D.
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
02/28/2012