DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020818/S-043 **SUPPLEMENT APPROVAL**

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

Dear Ms. Price:

Please refer to your supplemental new drug application dated March 12, 2009, received March 12, 2009, submitted under section 505(b)(i) of the Federal Food, Drug, and Cosmetic Act for Diovan HCT (valsartan/hydrochlorothiazide) 80/12.5, 160/12.5, 160/25, 320/12.5, and 320/25 mg Tablets.

This "Changes Being Effected" (CBE) supplemental new drug application provides for addition of the terms "vasculitis" and "syncope" to Section **6.2 Postmarketing Experience** and information on hyponatremia with carbamazepine to Section **7 DRUG INTERACTIONS**, **Hydrochlorothiaizide** of the Full Prescribing Information (FPI). The following changes are proposed:

1. Under Section **6.2 Postmarketing Experience**, the first sentence was changed from:

   [redacted] **(b) (4)**

   To:

   The following additional adverse reactions have been reported in valsartan or valsartan/hydrochlorothiazide postmarketing experience:

2. Under Section **6.2 Postmarketing Experience**, the following was added after the listing of "***Dermatologic:*** Alopecia;":

   Vascular: Vasculitis;

   Nervous System: Syncope.

3. Under Section **7 DRUG INTERACTIONS, Hydrochlorothiazide**, the following statement was added at the end of the section:

   Carbamazepine – May lead to symptomatic hyponatremia.

In addition, the following minor editorial change was noted under the **FULL PRESCRIBING INFORMATION: CONTENTS*** section:

1. The listing of "16. HOW SUPPLIED/STORAGE AND HANDLING" has been deleted. (Note: This listing should be re-added since it still appears in the FPI - see below.)

Minor editorial corrections in punctuation have also been made throughout the labeling.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the electronic content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format submitted on March 12, 2009.

At the time of your next printing, please make the following editorial corrections and report these changes in your next Annual Report:

1. Re-add the listing of "16. HOW SUPPLIED/STORAGE AND HANDLING" under the **FULL PRESCRIBING INFORMATION: CONTENTS*** section.

2. For all references throughout the FPI, please italicize the brackets and change the letter "S" in the word "See" to lowercase type.

3. Under Section **2.1 General Considerations**, *Hepatic impairment*, please change the reference at the end of this section from:

   (b) (4)

   To

   [see Warnings and Precautions (5.3)]

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

At the time of your next labeling change submission, please include the clinical pharmacology changes described below to update the information regarding metabolism (CYP 2C9 information) and disposition (transporter information) of valsartan based on published studies. These changes have been approved and implemented in your current Exforge HCT labeling (for the CYP 2C9 information) and your Diovan labeling (for the transporter information).

1. Under Section **7 DRUG INTERACTIONS**, **Valsartan**, the following paragraph should be 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 low extent of metabolism *[see Pharmacokinetics (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 should be changed from:

   [redacted] (b) (4)

   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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

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.
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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20818	SUPPL-43	NOVARTIS PHARMACEUTICALS CORP	DIOVAN HCT (VALSARTAN/HCTZ) TABLETS

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
04/21/2010