DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021990/S-007 **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 February 17, 2009, received February 17, 2009, submitted under section 505(b)(i) of the Federal Food, Drug, and Cosmetic Act for Exforge (amlodipine and valsartan) 5/160, 10/160, 5/320, and 10/320 mg Tablets.

This "Changes Being Effected" supplemental new drug application provides for addition of the term "vasculitis" to section **6.2 Postmarketing Experience** and information on "neutropenia" to section **7.4 Clinical Laboratory Test Findings** of the Full Prescribing Information (FPI). These changes were proposed to the Exforge labeling to be consistent with the information already approved in your Diovan labeling. The following changes are proposed:

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

   Vascular: Vasculitis

2. Under **7.4 Clinical Laboratory Test Findings**, the following was added at the end of the section:

   Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

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

1. The word order for the listing of section 5.3 has been changed from:

   5.3 Increased Angina and/or Myocardial Infarction

   To:

   5.3 Risk of Myocardial Infarction or Increased Angina

2. The listing of "6.2 Postmarketing Experience" 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 February 17, 2009.

At the time of your next printing, please re-add the listing of "6.2 Postmarketing Experience" under the **FULL PRESCRIBING INFORMATION: CONTENTS*** section. This change may be reported in your next Annual Report.

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 (transporters 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). In addition, please re-locate the sentence in the FPI under section **7.3 Drug/Food Interactions** to section **12.3 Pharmacokinetics** as described below.

1. Under **7.2 CYP 450 Interactions**, the following paragraph should be changed from:

   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:

   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, Valsartan (12.3)*].

2. Under **7.3 Drug/Food Interactions**, the entire section should be changed from:

   7.3 Drug/Food Interactions
   Studies with Exforge
   The bioavailabilities of amlodipine and valsartan are not altered by the co-administration of food.

   To:

   7.3 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.

3. Under the **FULL PRESCRIBING INFORMATION: CONTENTS*** section, the listing for section 7.3 should be changed from:

   7.3 Drug/Food Interactions

   To:

   7.3 Transporters

4. Under **12.3 Pharmacokinetics**, **Valsartan**, the last sentence of the third paragraph should be changed from:

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

   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.

5. Under **12.3 Pharmacokinetics**, **Exforge**, the following sentence should be added as the last sentence of the paragraph:

   The bioavailabilities of amlodipine and valsartan are not altered by the co-administration of food.

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-21990	SUPPL-7	NOVARTIS PHARMACEUTICALS CORP	EXFORGE(AMLODIPINE BESYLATE & VALSARTAN

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
03/30/2010