DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021990/S-013

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals
Attention: Nancy Price
Global Program Regulatory Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Price:

Please refer to your Supplemental New Drug Application (sNDA) dated April 1, 2011, received April 1, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exforge (amlodipine/valsartan) 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg Tablets.

This "Changes Being Effected" supplemental new drug application provides for labeling revised as follows:

1. The **HIGHLIGHTS/RECENT MAJOR CHANGES**, section was deleted.

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

   NSAID use may lead to increased risk of renal impairment and loss of anti-hypertensive effect

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

   7.3 Drug/Food Interactions

   To:

   7.3 Transporters

4. Under **DRUG INTERACTIONS,** the following section was added:

   Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
   In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors with angiotensin II receptor antagonists, including

valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

5. Under **DRUG INTERACTIONS/CYP 450 Interactions,** the first paragraph was 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 (12.3)]*.

6. Under **DRUG INTERACTIONS/Transporters,** the first paragraph was 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.

7. Under **CLINICAL PHARMACOLOGY/Phamacokinetics/Valsartan**, the last sentence of the third paragraph was 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.

8. Under **CLINICAL PHARMACOLOGY/Phamacokinetics/Valsartan**, the following sentence was added as the last sentence of the paragraph:

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

9. Under **FDA APPROVED PATIENT LABELING**/PATIENT INFORMATION/What should I tell my doctor before taking EXFORGE?, under the second paragraph, a fifth bullet was added:
   - Nonsteroidal anti-inflammatory drugs (like ibuprofen or naproxen)

The revision date and version number were updated.

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).

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, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE(S):
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
05/31/2011