DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-314/S-020

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy Price
One Health Plaza
Building 125/2113A
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on January 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) Tablets, 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 10/320/25 mg.

This "Prior Approval" supplemental new drug application provides for an update to sections **7 DRUG INTERACTIONS**, **Valsartan**, *Potassium* and **8 USE IN SPECIFIC POPULATIONS, Geriatric Use** [8.5] and **Hepatic Impairment** [8.7]. In addition, the information in sections **7 DRUG INTERACTIONS** and **12 CLINICAL PHARMACOLOGY** has been updated to be consistent with the recently approved package insert for Norvasc (NDA 19-787/S-059, approved on March 23, 2015). Other minor changes have been made. The changes are as follows (additions are shown as underlined text and deletions are shown as ~~strike-through text~~):

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

1. The route of administration ("for oral use") was added to the product title line.

2. Under **USE IN SPECIFIC POPULATIONS**, the following changes were made:

> **Nursing Mothers:** Avoid use while nursing – discontinue either nursing or drug (8.3)
> **Geriatric Patients:** Not recommended for initial therapy (8.5)
> **Hepatic Impairment:** Not recommended for initial therapy (8.7)

In **FULL PRESCRIBING INFORMATION**

3. Under section **7 DRUG INTERACTIONS**, the following changes were made:

> **7 DRUG INTERACTIONS**
>
> No drug interaction studies have been conducted with Exforge HCT and other drugs, although studies have been conducted with the individual components. A pharmacokinetic drug-drug interaction study has been conducted to address the potential for pharmacokinetic interaction between the triple combination, Exforge HCT, and the corresponding 3 double combinations. No clinically relevant interaction was observed.

Amlodipine

Impact of other Drugs on Amlodipine

CYP3A Inhibitors

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment *[see Clinical Pharmacology (12.3)]*.

CYP3A Inducers

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

Sildenafil

Monitor for hypotension when sildenafil is co-administered with amlodipine *[see Clinical Pharmacology (12.2)]*.

Impact of Amlodipine on other Drugs

Simvastatin

Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily *[see Clinical Pharmacology (12.3)]*.

Immunosuppressants

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate *[see Clinical Pharmacology (12.3)]*.

~~***Simvastatin:*** Coadministration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.~~

~~***CYP3A4 Inhibitors:*** Coadministration with CYP3A inhibitors (moderate and strong) result in increased systemic exposure to amlodipine warranting dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is coadministered with CYP3A4 inhibitors to determine the need for dose adjustment.~~

~~***CYP3A4 Inducers:*** No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be monitored when amlodipine is coadministered with CYP3A4 inducers.~~

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

In vitro metabolism studies have indicated that CYP450 mediated drug interaction between valsartan and coadministered drugs are unlikely because of the low extent of metabolism *[see Pharmacokinetics – Valsartan, (12.3)]*.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

Potassium: Concomitant 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 or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

4. Under subsection **8.5 Geriatric Use**, **Amlodipine**, the following changes were made:

8.5 Geriatric Use

Amlodipine: Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60% *[see Clinical Pharmacology (12.3)]*. The recommended starting dose of amlodipine 2.5 mg is not an available strength with Exforge HCT *[see Clinical Studies (14)]*.

~~Exposure to amlodipine is increased in elderly patients, thus consider lower initial doses of Exforge HCT [see Clinical Pharmacology (12.3)].~~

~~In controlled clinical trials, 82 hypertensive patients treated with Exforge HCT were ≥65 years and 13 were ≥75 years. No overall differences in the efficacy or safety of Exforge HCT were observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.~~

5. Under subsection **8.7 Hepatic Impairment**, Amlodipine, the following changes were made:

Amlodipine

Exposure to amlodipine is increased in patients with hepatic insufficiency~~, thus consider using lower doses of Exforge HCT~~ The recommended initial dose of amlodipine in patients with hepatic impairment is 2.5 mg, which is not an available strength with Exforge HCT *[see Clinical Pharmacology (12.3)]*.

6. Under subsection **12.2 Pharmacodynamics**, **Amlodipine**, the following has been added to the end of this subsection:

Drug Interactions

Sildenafil
When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect *[see Drug Interactions (7)]*.

7. Under subsection **12.3 Pharmacokinetics**, **Drug Interactions**, **Amlodipine**, the following changes have been made:

Drug Interactions

Amlodipine:

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Impact of other drugs on amlodipine

Co-administered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent *[see Drug Interactions (7)]*.

Impact of amlodipine on other drugs

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone *[see Drug Interactions (7)]*.

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine *[see Drug Interactions (7)]*.

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5- to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs *[see Drug Interactions (7)]*.

~~*Cimetidine:* Coadministration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.~~

~~*Grapefruit juice:* Coadministration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.~~

~~*Maalox® (antacid):* Coadministration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.~~

~~*Sildenafil:* A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.~~

~~*Atorvastatin:* Coadministration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.~~

~~*Digoxin:* Coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.~~

~~*Ethanol (alcohol):* Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.~~

~~*Warfarin:* Coadministration of amlodipine with warfarin did not change the warfarin prothrombin response time.~~

~~*Simvastatin:* Coadministration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.~~

~~*CYP3A4 Inhibitors:* Coadministration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin coadministration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.~~

8. Under section **17 PATIENT COUNSELING INFORMATION,** the following sentence was added after **Information for Patients**:

   Advise the patient to read the FDA-approved patient labeling (Patient Information).

9. Minor editorial and formatting corrections were made throughout the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and **FULL PRESCRIBING INFORMATION**.

10. The revision dates have been updated.

APPROVAL & LABELING

We have completed our review of this supplemental application. 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 and 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 that includes labeling changes 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}

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

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
07/28/2015