DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021990/S-018

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy Price
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms Price:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received March 9, 2012, 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.

We acknowledge your amendment dated June 29, 2012.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added:

Indications and Usage: Benefits of lowering blood pressure (1)	12/2011
Contraindications: Known hypersensitivity (4)	XX/2012
Boxed Warning: Fetal Toxicity	01/2012
Warnings and Precautions: Fetal Toxicity (5.1)	01/2012

2. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the following text was added/deleted:

~~• Avoid fetal or neonatal exposure (5.1)~~
• ~~Assess for h~~ Hypotension: Correct volume depletion prior to initiation (5.2)
• ~~Warn patients with severe obstructive coronary artery disease about the risk of myocardial infarction or i~~Increased angina and/or myocardial infarction(5.3)
~~• Titrate slowly in patients with impaired hepatic (5.4) or severely impaired renal (5.5) function~~
- Monitor renal function and potassium in susceptible patients (5.4, 5.5)

3. Under **CONTRAINDICATIONS,** the following text was added/deleted:

~~None.~~ Do not use in patients with known hypersensitivity to any component.

4. Under **WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

5.3 Risk of Myocardial Infarction or Increased Angina

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

~~Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.~~

5.4 Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g. patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Exforge. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Exforge.

5.5 Hyperkalemia

Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

Some patients with heart failure have developed increases in potassium with valsartan therapy. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of Exforge may be required. *[see Adverse Reactions (6.1)]*.

~~**5.4 Impaired Hepatic Function**~~

~~***Studies with Amlodipine:*** Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) is 56 hours in patients with impaired hepatic function, therefore, caution should be exercised when administering amlodipine to patients with severe hepatic impairment.~~

~~***Studies with Valsartan:*** As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients.~~

~~**5.5 Impaired Renal Function - Hypertension**~~

~~In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may occur particularly in volume-depleted patients. In~~

~~patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.~~

~~**5.6 Congestive Heart Failure**~~

~~***Studies with Amlodipine:*** In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.~~

~~***Studies with Valsartan:*** Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.~~

5. Under **ADVERSE REACTIONS**, the following text was added:

Studies with Exforge:

Exforge has been evaluated for safety in over 2,600 patients with hypertension; over 1,440 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least one year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The hazards [*see Warnings and Precautions(5)*] of valsartan are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter.

6. Under **ADVERSE REACTIONS/Clinical Trials Experience**, the following text was added:

Studies with Exforge:

Exforge has been evaluated for safety in over 2,600 patients with hypertension; over 1,440 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least one year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The hazards [*see Warnings and Precautions(5)*] of valsartan are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter.

Clinical Lab Test Findings:

Creatinine: In hypertensive patients, greater than 50% increases in creatinine occurred in 0.4% of patients receiving Exforge and 0.6% receiving placebo. In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Exforge-treated patients.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 2.8% of Exforge-treated patients compared to 3.4% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In hypertensive patients, greater than 50% increases in BUN were observed in 5.5% of Exforge-treated patients compared to 4.7% of placebo-treated patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

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

7. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following text was added:

Blood and Lymphatic: ~~There are very rare reports of thrombocytopenia.~~Decrease in hemoglobin, decrease in hematocrit, neutropenia,

Renal: Impaired renal function, renal failure

8. Under **DRUG INTERACTIONS**, the following text was added/deleted:

7.1 Drug/Drug Interactions
No drug interaction studies have been conducted with Exforge and other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below:

Studies with Amlodipine

***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.

***CYP3A4 Inhibitors**:* Co-administration with CYP3A4 inhibitors (moderate and strong) result in increased systemic exposure to amlodipine warranting dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered 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 co-administered with CYP3A4 inducers.

~~In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.~~
~~***Cimetidine:*** Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.~~
~~***Grapefruit juice:*** Co-administration 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):*** Co-administration 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 (Viagra®**) 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:*** Co-administration 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:*** Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.~~
~~***Warfarin:*** Co-administration of amlodipine with warfarin did not change 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. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.~~

Studies with Valsartan
No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered 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.

Warfarin: Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

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.

***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 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.

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, Valsartan (12.3)]*. ~~As with other drugs that block angiotensin II or its effects, concomitant use of 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.~~

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.

~~**7.2 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, Valsartan* (12.3)]. As with other drugs that block angiotensin II or its effects, concomitant use of 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.~~

~~**7.4 Clinical Laboratory Findings**~~

~~***Creatinine:*** In hypertensive patients, greater than 50% increases in creatinine occurred in 0.4% of patients receiving Exforge and 0.6% receiving placebo. In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.~~

~~***Liver Function Tests:*** Occasional elevations (greater than 150%) of liver chemistries occurred in Exforge-treated patients.~~

~~***Serum Potassium:*** In hypertensive patients, greater than 20% increases in serum potassium were observed in 2.8% of Exforge-treated patients compared to 3.4% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum~~

~~potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.~~

~~***Blood Urea Nitrogen (BUN):*** In hypertensive patients, greater than 50% increases in BUN were observed in 5.5% of Exforge-treated patients compared to 4.7% of placebo-treated patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.~~

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

9. Under **USE IN SPECIFIC POPULATIONS**, the following text was added:

8.6 Renal Impairment
Safety and effectiveness of Exforge in patients with severe renal impairment (CrCl< 30 mL/min) have not been established. No dose adjustment is required in patients with mild (60-90 mL/min) or moderate (CrCl 30-60) renal impairment.

8.7 Hepatic Impairment

Amlodipine
Exposure to amlodipine is increased in patients with hepatic insufficiency, thus consider using lower doses of Exforge HCT *[see Clinical Pharmacology (12.3)]*

Valsartan
No dose adjustment is necessary for patients with mild-to-moderate disease. No dosing recommendations can be provided for patients with severe liver disease.

10. Under **OVERDOSAGE**, the following text was added/deleted:

Information on Amlodipine
Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.~~Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted.~~

If massive overdose should occur, initiate active cardiac and respiratory monitoring ~~should be instituted~~. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. ~~Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade.~~ As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Information on Valsartan
Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be peripheral vasodilation, hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

11. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/deleted:

Special Populations

Geriatric
Studies with Amlodipine*:* Elderly patients have decreased clearance of amlodipine with a resulting increase in peak plasma levels, elimination half-life and AUC. ~~Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%-60%; therefore a lower initial dose of amlodipine may be required.~~***~~Studies with Valsartan~~****~~:~~* ~~Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary.~~

Drug Interactions

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

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration 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): Co-administration 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 (Viagra®**) 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: Co-administration 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: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: Co-administration of amlodipine with warfarin did not change 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. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

CYP3A4 Inhibitors*:* Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodpidine in elderly hypertensives 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 inhbitors of CYP3A4 (e.e., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

12. In **FDA-Approved Patient Labeling,** under **What should I tell my doctor before taking EXFORGE?**, the following bullet was added:

- have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue, throat, and may cause difficulty breathing.

Especially tell your doctor if you take:

- simvastatin or other cholesterol lowering medicine
- other medicines for high blood pressure or a heart problem
- water pills (diuretics)
- potassium supplements. Your doctor may check the amount of potassium in your blood periodically.
- a salt substitute. Your doctor may check the amount of potassium in your blood periodically.
- nonsteroidal anti-inflammatory drugs (like ibuprofen or naproxen)
- medicines used to prevent and treat fungal skin infections (such as Ketoconazole, itraconazole)

- medicines used to treat bacterial infections (such as clarithromycin, telithromycin)
- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporin) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.

13. In **FDA-Approved Patient Labeling,** under **What are the possible side effects of EXFORGE?**, the following text was added/deleted:

    - **laboratory blood test changes in people with ~~congestive~~ heart failure**. Some people with ~~congestive~~ heart failure who take valsartan, one of the medicines in EXFORGE, have changes in blood tests including increased potassium and decreased kidney function.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, as amended, 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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:
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
09/28/2012