



NDA 200045/S-011; S-013

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Leigh Strachan
Global Program Regulatory Affairs, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Strachan:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received March 9, 2012 (S-011), and August 1, 2012 (S-013), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amturnide (aliskiren/amlodipine besylate/hydrochlorothiazide) 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, and 300/10/25 mg Tablets.

We acknowledge receipt of your amendment dated May 1, 2012 (S-011).

These "Prior Approval" supplemental new drug applications provide 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:

Boxed Warning: Fetal Toxicity	02/2012
Contraindications: Concomitant use with ARBs or ACEIs in diabetes (4)	03/2012
<u>Contraindications (4)</u>	<u>09/2012</u>
Warnings and Precautions (5.1, 5.13)	02/2012
Warnings and Precautions (5.2, 5.4, 5.6, 5.10)	03/2012
<u>Warnings and Precautions (5.4, 5.5)</u>	<u>09/2012</u>
<u>Warnings and Precautions (5.3)</u>	<u>09/2012</u>

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

- Do not use with angiotensin receptor blockers (ARBs) or ACE inhibitors (ACEI) in patients with diabetes (4)
- Anuria (4)
- Hypersensitivity to sulfonamide-derived drugs or to any of the components (4)

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

- Avoid concomitant use with ARBs or ACEIs in patients with renal impairment (GFR<60 mL/min) (5.2)
- Anaphylactic Reactions and Head and Neck Angioedema: Discontinue Amturnide and monitor until signs and symptoms resolve. (5.3)
- Hypotension: Correct volume depletion prior to initiation. (5.4)

- Increased angina or myocardial infarction may occur upon dosage initiation or increase in amlodipine. (5.5)
- Impaired renal function: Monitor serum creatinine periodically (5.6)
- HCTZ may exacerbate or activate systemic lupus erythematosus. (5.9, 5.8)
- Hyperkalemia: Monitor potassium levels periodically. (5.11, 5.10)
- Acute myopia and secondary angle closure glaucoma: Discontinue HCTZ. (5.13, 5.12)
- Hypersensitivity Reactions: May occur from HCTZ component. (5.8, 5.7)

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

Do not use aliskiren with ARBs or ACEIs in patients with diabetes [see Warnings and Precautions (5.2), Clinical Studies Trials (14.2)].

Amturnide is contraindicated in patients with anuria or hypersensitivity to sulfonamide-derived drugs like HCTZ or to any of the components [see *Warnings and Precautions* (5.8) and *Adverse Reactions* (6.1)]. Hypersensitivity reactions may range from urticaria to anaphylaxis.

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

5.3 Head and Neck Angioedema

Aliskiren

Hypersensitivity reactions such as anaphylactic reactions and angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. Anaphylactic reactions have been reported from post-marketing experience with unknown frequency. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation and appropriate monitoring measures since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) and measures to ensure a patent airway may be necessary.

Discontinue Amturnide immediately in patients who develop anaphylactic reactions or angioedema, and do not re-administer.

Amlodipine besylate

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

5.5 Risk of Myocardial Infarction or Increased Angina

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly with severe obstructive coronary artery disease. Rarely, initiation or change to the dose of a calcium channel blocker has resulted in the development of documented increased frequency, duration or severity of angina or acute myocardial infarction, particularly in patients with severe obstructive coronary artery disease. The mechanism of this effect has not been elucidated.

5.7 Patients with Heart Failure

~~Amlodipine has not been studied in patients with heart failure.~~

~~Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitors, 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 left ventricular ejection fraction.~~

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

Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization.

Peripheral edema, severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

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

Amlodipine

~~In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.~~

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

CYP3A4 Inhibitors: Co-administration 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 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.

8. Under **USE IN SPECIFIC POPULATIONS**, the following text was added/deleted:

Amlodipine

No evidence of teratogenicity or embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. In developmental toxicity studies, pregnant rats and rabbits received oral amlodipine maleate during organogenesis at doses approximately 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area (mg/m²), respectively, in rats and rabbits. (Actual animal doses were up to 10 mg/kg/day.) No evidence of teratogenicity or other embryofetal toxicity was observed. However, litter size was decreased approximately 50% and the number of intrauterine deaths was increased approximately 5-fold for rats receiving amlodipine maleate at doses approximately 10 times the MRHD based on body surface area (mg/m²) for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

8.5 Geriatric Use

As individual components, exposure to aliskiren, amlodipine and hydrochlorothiazide is increased in elderly patients, thus consider lower initial doses of Amturnide [see *Clinical Pharmacology* (12.3)].

In the short-term controlled clinical trial of Amturnide, 19% of patients treated with Amturnide were ≥ 65 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

~~Patients > 75 years of age should start amlodipine at 2.5 mg, which is not available with Amturnide.~~

8.6 Hepatic Impairment

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

Hydrochlorothiazide

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

8.7 Renal Impairment

Exposure to hydrochlorothiazide increases in patients with renal insufficiency, thus consider using lower doses of Amturnide [see Clinical Pharmacology (12.3)].

Safety and effectiveness of Amturnide in patients with severe renal impairment (creatinine clearance < 30 mL/min) have not been established as these patients were excluded in clinical trials [see Warnings and Precautions (5.6), Clinical Pharmacology (12.3) and Clinical Studies (14)].

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

8.7 Hepatic Impairment

Aliskiren

~~No dose adjustment is necessary for patients with mild to severe liver disease.~~

Hydrochlorothiazide

~~Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.~~

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

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. In humans, experience with intentional overdosage of amlodipine is limited. ~~Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third patient (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 were noted.~~

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

If massive overdose occurs, ~~institute~~ initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. If hypotension occurs, ~~initiate~~ provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine), 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.

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

Amlodipine

Peak plasma concentrations of amlodipine are reached 6-12 hours after an oral administration of amlodipine. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food. ~~Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.~~

The apparent volume of distribution of amlodipine is about 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Metabolism and Elimination

Amlodipine

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism, with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination of amlodipine from the plasma is biphasic, with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels are reached after once-daily dosing for 7-8 days.

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

Amlodipine

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 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.

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

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.

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 CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

12. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/Special Populations**, the following text was added/deleted:

Geriatric Patients

Impact of aging on aliskiren pharmacokinetics has been assessed. When compared to young adults (18-40 years), aliskiren mean AUC and C_{max} in elderly subjects (> 65 years) are increased by 57% and 28%, respectively. In the elderly, clearance of amlodipine is decreased with resulting increases in peak plasma levels, elimination half-life and area-under-the-plasma-concentration curve. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers [see Use in Specific Populations (8.5)].

~~Aliskiren~~

~~The pharmacokinetics of aliskiren were studied in the elderly (>65 years). Exposure (measured by AUC) is increased in elderly patients.~~

~~Amlodipine~~

~~Elderly patients have decreased clearance of amlodipine, with a resulting increase in AUC of approximately 40%-60%.~~

~~Hydrochlorothiazide~~

~~Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.~~

Race

With Amlodipine, pharmacokinetic differences due to race have not been studied. The pharmacokinetic differences among Blacks, Caucasians, and Japanese are minimal with aliskiren therapy.

Hepatic Impairment

The pharmacokinetics of aliskiren is not significantly affected in patients with mild-to-severe liver disease. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60% [see Warnings and Precautions (5.6) and Use in Specific Populations (8.6)].

Renal Impairment

~~Aliskiren~~

~~The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal impairment. Rate and extent of exposure (AUC and C_{max}) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment [see Use in Specific Populations (8.6)].~~

The pharmacokinetics of aliskiren following administration of a single oral dose of 300 mg was evaluated in patients with End Stage Renal Disease (ESRD) undergoing hemodialysis. When compared to matched healthy subjects, changes in the rate and extent of aliskiren exposure (C_{max} and AUC) in ESRD patients undergoing hemodialysis was not clinically significant. Timing of hemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. ~~Therefore, no dose adjustment is warranted in ESRD patients receiving hemodialysis.~~

~~Amlodipine~~

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. ~~Patients with renal failure may therefore receive the usual initial dose.~~

Hydrochlorothiazide

In a study in individuals with impaired renal function, the mean elimination half-life of hydrochlorothiazide was doubled in individuals with mild/moderate renal impairment ($30 < \text{CLcr} < 90 \text{ mL/min}$) and tripled in severe renal impairment ($\leq 30 \text{ mL/min}$), compared to individuals with normal renal function ($\text{CLcr} > 90 \text{ mL/min}$) [*see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)6*].

Hepatic Impairment

Aliskiren

~~The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to-severe liver disease [*see Use in Specific Populations (8.7)*].~~

Amlodipine

~~Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%–60%. A lower initial dose of amlodipine is required for patients with severe hepatic impairment [*see Use in Specific Populations (8.7)*].~~

13. Under **NONCLINICAL TOXICOLOGY**, the following text was added/~~deleted~~ from the fifth and seventh paragraphs, respectively:

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m^2 basis, similar to the maximum recommended human dose (MRHD) of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about ~~two and half times~~ twice the MRHD. (~~Calculations are based on a 60 kg patient.~~)

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about ~~408~~ times the MRHD of 10 mg/day on a mg/m^2 basis).

14. Under **PATIENT COUNSELING INFORMATION**, the following text was added:

Anaphylactic Reactions and Angioedema

Advise patients to report immediately any signs or symptoms suggesting a severe allergic reaction (difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain) or angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no

more drug until they have consulted with the prescribing physician. Angioedema, including laryngeal edema, may occur at any time during treatment with Amturnide.

15. In the **FDA-Approved Patient Labeling**/Before taking Amturnide, tell your doctor if you:, a fifth bullet was added:
- suffer from heart disorders or if you experienced a heart attack
16. In the **FDA-Approved Patient Labeling**/Especially tell your doctor if you are taking:, the following text was added:
- cholesterol lowering medicines
 - simvastatin (Zocor[®]) or atorvastatin (Lipitor[®])
 - medicines used to treat AIDS or HIV infections (such as ritonavir, indinavir)
17. In the **FDA-Approved Patient Labeling**/What are the possible side effects of Amturnide?, the following text was added/deleted:
- **Severe Allergic Reactions and Angioedema.** Aliskiren, one of the medicines in Amturnide, can cause difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain (signs of a severe allergic reaction). ~~Aliskiren, one of the medicines in Amturnide~~ can also cause swelling of your face, lips, tongue, throat, arms and legs, or the whole body (signs of angioedema). Get medical help right away and tell your doctor if you get any one or more of these symptoms. Serious allergic reactions can happen at any time while you are taking Amturnide.
18. There are multiple editorial revisions throughout the label.
19. The revision date and version number were updated.

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

We have completed our review of these supplemental applications, as amended, and they are 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, PharmD.
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