DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021093/S-018 **SUPPLEMENT APPROVAL**

AstraZeneca
Attention: Ian Wogan
Director, Regulatory Affairs
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Wogan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 9, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atacand HCT (candesartan cilexetil/hydrochlorothiazide) 16/12.5 mg, 32/12.5 mg, and 32/25 mg Tablets.

We acknowledge your amendments dated March 7, and April 4, 2013.

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. Under **CLINICAL PHARMACOLOGY,*Renal Insufficiency***, the following text was added/~~deleted~~:

   In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m^2) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. ~~No initial dosage adjustment is necessary in patients with renal insufficiency.~~

   Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours. In a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours. (See DOSAGE AND ADMINISTRATION.)

   Safety and effectiveness of ATACAND HCT 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.

2. Under **CLINICAL PHARMACOLOGY, *Hepatic Insufficiency***, the following text was added/~~deleted~~:

   The pharmacokinetics of candesartan were compared in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment to matched healthy volunteers following a single dose of 16 mg candesartan cilexetil. The AUC for candesartan in patients with mild and moderate hepatic impairment was increased 30% and 145% respectively. The C_{max} for candesartan was increased 56% and 73% respectively. The pharmacokinetics of candesartan

in severe hepatic impairment have not been studied. No dose adjustment is recommended for patients with mild hepatic impairment. In patients with moderate hepatic impairment, ATACAND HCT is not recommended for initiation because the appropriate starting dose, 8 mg, cannot be given ~~consideration should be given to initiation of ATACAND at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, ATACAND HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given.~~ (See **DOSAGE AND ADMINISTRATION**).

Monitor patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

~~Thiazide diuretics should be used with caution in patients with hepatic impairment. (See DOSAGE AND ADMINISTRATION.)~~

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

ATACAND HCT is contraindicated in patients who are hypersensitive to ~~any component of this product~~ candesartan, to hydrochlorothiazide or to other sulfonamide-derived drugs.

Do not co-administer aliskiren with ATACAND HCT in patients with diabetes (see PRECAUTIONS, Drug Interactions).

~~Because of the hydrochlorothiazide component, this product~~ ATACAND HCT is contraindicated in patients with anuria ~~or hypersensitivity to other sulfonamide derived drugs~~.

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

Hypotension~~ in Volume and Salt Depleted Patients~~

ATACAND HCT can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Patients with symptomatic hypotension may require temporarily reducing the dose of ATACAND HCT or volume repletion. Volume and/or salt depletion should be corrected before initiating therapy with ATACAND HCT.

In patients with heart failure, ATACAND HCT may cause excessive hypotension, which may lead to oliguria, azotemia, and (rarely) with acute renal failure and death (see WARNINGS, Impaired Renal Function). In such patients, ATACAND HCT therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of candesartan or diuretic is increased.

~~Based on adverse events reported from all clinical trials of ATACAND HCT, excessive reduction of blood pressure was rarely seen in patients with uncomplicated hypertension treated with candesartan cilexetil and hydrochlorothiazide (0.4%). Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium- depletion, eg, in patients treated vigorously with diuretics or in patients on dialysis. These conditions should be corrected prior to administration of ATACAND HCT, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).~~

~~If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a~~

~~contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.~~

Impaired Renal Function

Monitor renal function periodically in patients treated with ATACAND HCT. 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 heart failure, or volume depletion) may be at particular risk of developing oliguria, progressive azotemia, or acute renal failure on ATACAND HCT. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on ATACAND HCT.

Potassium Abnormalities

Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesema can result in hypokalemia which appears difficult to treat despite potassium repletion. Monitor serum electrolytes periodically. In clinical trials of various doses of candesartan cilexetil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.5% versus 2.1% for placebo; the incidence of hyperkalemia (serum potassium ≥5.7 mEq/L) was 0.4% versus 1.0% for placebo. No patient receiving ATACAND HCT 16-12.5 mg or 32-12.5 mg was discontinued due to increases or decreases in serum potassium.

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

~~Thiazide diuretics should be used with caution in~~Monitor patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

~~***Systemic Lupus Erythematosus***~~

~~Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.~~

~~*Lithium Interaction*~~

~~Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Hydrochlorothiazide, Lithium).~~

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

~~**General**~~ **Metabolic Disturbances**

~~**Candesartan Cilexetil–Hydrochlorothiazide**~~

~~In clinical trials of various doses of candesartan cilexetil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.5% versus 2.1% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% versus 1.0% for placebo. No patient receiving ATACAND HCT 16-12.5 mg or 32-12.5 mg was discontinued due to increases or decreases in serum potassium. Overall, the combination of candesartan cilexetil and hydrochlorothiazide had no clinically significant effect on serum potassium.~~
~~*Candesartan*~~

~~*Major Surgery/Anesthesia* – Hypotension may occur during major surgery and anesthesia in patients treated with angiotensin II receptor antagonists, including candesartan, due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.~~

~~**Hydrochlorothiazide**~~

~~Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.~~

~~All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.~~

~~Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (eg, increased ventricular irritability).~~

~~Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.~~

~~Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.~~

~~Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.~~

~~In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required.~~
~~Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.~~

~~The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.~~

~~If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.~~

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium. Avoid using ATACAND HCT in patients with hypercalcemia.

Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

~~Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.~~

~~Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.~~

~~Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.~~

~~***Impaired Renal Function***~~

~~**Candesartan Cilexetil**~~
~~As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with candesartan cilexetil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe congestive heart failure), 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 results may be anticipated in patients treated with candesartan cilexetil. (See CLINICAL PHARMACOLOGY, Special Populations.)~~

~~In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of candesartan cilexetil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.~~

~~**Hydrochlorothiazide**~~
~~Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.~~

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

~~**Candesartan Cilexetil**~~
~~Based on pharmacokinetic data significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment have been demonstrated. (See CLINICAL PHARMACOLOGY, Special Populations.)~~

6. Under **PRECAUTIONS**, **Information for Patients** the following text was added/~~deleted~~:

Tell ~~A~~ patients receiving ATACAND HCT ~~should be cautioned~~ that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. Tell ~~T~~he patients ~~should be told~~ that if syncope occurs, discontinue ATACAND HCT ~~should be discontinued~~ until the physician has been consulted.

Tell a~~A~~ll patients ~~should be cautioned~~ that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements Hyperkalemia

Tell ~~A~~ patients receiving ATACAND HCT ~~should be told~~ not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

7. Under **PRECAUTIONS, Drug Interactions**, the following text was added/~~deleted~~:

~~**Candesartan Cilexetil**~~

~~No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers.~~ Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Interactions common to both Candesartan Cilexetil and Hydrochlorothiazde

Lithium − Renal clearance of lithium is reduced by thiazides and increases the risk of lithium toxicity. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with candesartan cilexetil. ~~so careful monitoring of serum lithium levels is recommended during concomitant use.~~ Monitor serum lithium levels.

Interactions with Candesartan Cilexetil

Dual Blockade of the Renin-Angiotensin System (RAS)
Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on ATACAND HCT and other agents that affect the RAS.

Do not co-administer aliskiren with ATACAND HCT in patients with diabetes. Avoid use of aliskiren with ATACAND HCT in patients with renal impairment (GFR <60 ml/min) (see CONTRAINDICATIONS).

Interactions with Hydrochlorothiazide

~~When administered concurrently the following drugs may interact with thiazide diuretics:~~

~~*Other antihypertensive drugs* − Additive effect or potentiation.~~

~~*Cholestyramine and colestipol resins Ion Exchange resins* − Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.~~ Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively. Stagger the dosage of hydrochlorothiazide and ion exchange resins such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins.

~~*Corticosteroids, ACTH* – Intensified electrolyte depletion, particularly hypokalemia.~~

~~*Pressor amines (eg, norepinephrine)* – Possible decreased response to pressor amines but not sufficient to preclude their use.~~

Skeletal muscle relaxants, nondepolarizing (eg, tubocurarine) −Possible increased responsiveness to muscle relaxants such as curare derivatives.

Digitalis: Thiazide-induced hypokalemia or hypomagnesemia may predispose to digoxin toxicity.

~~*Lithium* – Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with ATACAND HCT.~~

~~*Non-steroidal Anti-inflammatory Drugs* – In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when ATACAND HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.~~

8. Under **PRECAUTIONS**, the following section was ~~deleted~~:

~~***Geriatric Use***~~

~~Of the total number of subjects in all clinical studies of ATACAND HCT (2831), 611 (22%) were 65 and over, while 94 (3%) were 75 and over. 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.~~

~~Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.~~

9. Under **ADVERSE REACTIONS**, the following text was added/~~deleted~~:

~~The frequency of headache was greater than 2% (2.9%) in patients treated with ATACAND HCT but was less frequent than the rate in patients treated with placebo (5.2%).~~
~~Other adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the more than 2800 patients worldwide treated with ATACAND HCT included:~~***Body as a Whole:*** ~~inflicted injury, fatigue, pain, chest pain, peripheral edema, asthenia;~~ ***Central and Peripheral Nervous System:*** ~~vertigo, paresthesia, hypesthesia;~~ ***Respiratory System Disorders:*** ~~bronchitis, sinusitis, pharyngitis, coughing, rhinitis, dyspnea;~~ ***Musculoskeletal System Disorders:*** ~~arthralgia, myalgia, arthrosis, arthritis, leg cramps, sciatica;~~ ***Gastrointestinal System Disorders:*** ~~nausea, abdominal pain, diarrhea, dyspepsia, gastritis, gastroenteritis, vomiting;~~ ***Metabolic and Nutritional Disorders:*** ~~hyperuricemia, hyperglycemia, hypokalemia, increased BUN, creatine phosphokinase increased;~~ ***Urinary System Disorders:*** ~~urinary tract infection, hematuria, cystitis;~~ ***Liver/Biliary System Disorders:*** ~~hepatic function abnormal, increased transaminase levels;~~ ***Heart Rate and Rhythm Disorders:*** ~~tachycardia, palpitation, extrasystoles, bradycardia;~~ ***Psychiatric Disorders:*** ~~depression, insomnia, anxiety;~~ ***Cardiovascular Disorders:*** ~~ECG abnormal;~~ ***Skin and Appendages Disorders:*** ~~eczema, sweating increased, pruritus, dermatitis, rash;~~ ***Platelet/Bleeding-Clotting Disorders:*** ~~epistaxis;~~ ***Resistance Mechanism***

~~***Disorders:*** infection, viral infection; ***Vision Disorders:*** conjunctivitis; ***Hearing and Vestibular Disorders:*** tinnitus.~~

~~Reported events seen less frequently than 0.5% included angina pectoris, myocardial infarction and angioedema.~~

~~**Candesartan Cilexetil**~~

~~Other adverse experiences that have been reported with candesartan cilexetil, without regard to causality, were: ***Body as a Whole:*** fever; ***Metabolic and Nutritional Disorders:*** hypertriglyceridemia; ***Psychiatric Disorders:*** somnolence; ***Urinary System Disorders:*** albuminuria.~~

10. Under **ADVERSE REACTIONS, Postmarketing Experience**, the following text was added/~~deleted~~:

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Immunologic: Angioedema

Metabolic and Nutritional Disorders: hyperkalemia, hyponatremia.

~~**Renal**: renal impairment, renal failure~~

Respiratory System Disorders: Cough

Skin and Appendages Disorders: Pruritus, rash and urticaria.

~~***Body As A Whole:*** weakness; ***Cardiovascular:*** hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs); ***GastrointestinalDigestive:***~~ pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, constipation, gastric irritation, anorexia;

~~***Metabolic:*** electrolyte imbalance~~

~~***Nervous System/Psychiatric:*** restlessness; ***Renal:*** renal failure, renal dysfunction, interstitial nephritis~~

~~***Laboratory Test Findings***~~

~~In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of ATACAND HCT.~~

~~*Creatinine, Blood Urea Nitrogen* – Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently. One patient was discontinued from ATACAND HCT due to increased BUN. No patient was discontinued due to an increase in serum creatinine.~~

~~*Hemoglobin and Hematocrit* – Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 g/dL and 0.4 volume percent, respectively) were observed in patients treated with ATACAND HCT, but were rarely of clinical importance.~~

~~*Potassium* – A small decrease (mean decrease of 0.1 mEq/L) was observed in patients treated with ATACAND HCT. In placebo-controlled trials, hypokalemia was reported in 0.4% of patients treated with ATACAND HCT as compared to 1.0% of patients treated with hydrochlorothiazide or 0.2% of patients treated with placebo.~~

~~*Liver Function Tests* – Occasional elevations of liver enzymes and/or serum bilirubin have occurred.~~

11. Under **DOSAGE AND ADMINSTRATION**, the following text was added/~~deleted~~:

Use in Renal Impairment: Dosing recommendations for ATACAND HCT in patients with creatinine clearance < 30 mg/min cannot be provided (see SPECIAL POPULATIONS, Renal Insufficiency).

Use in moderate to severe Hepatic Impairment: ATACAND HCT is not recommended for initiation because the appropriate starting dose, 8 mg, cannot be given. (see SPECIAL POPULATIONS, Hepatic Insufficiency).

~~To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.~~

~~The side effects (See WARNINGS) of candesartan cilexetil are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (eg, pancreatitis), the former much more common than the latter.~~

~~Therapy with any combination of candesartan cilexetil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.~~

~~**Patients with Renal Impairment:** The usual regimens of therapy with ATACAND HCT may be followed as long as the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so ATACAND HCT is not recommended.~~

~~**Patients with Hepatic Impairment:** The usual regimens of therapy with ATACAND HCT may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, ATACAND HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given. (See **CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency**).~~

~~Thiazide diuretics should be used with caution in patients with hepatic impairment; therefore, care should be exercised with dosing of ATACAND HCT.~~

12. 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 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, 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
04/26/2013