



NDA 020033/S-043

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Yifeng Jia  
Drug Regulatory Manager  
One Health Plaza  
East Hanover, NJ 07936

Dear Dr. Jia:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 9, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lotensin HCT (benazepril HCl and hydrochlorothiazide) 5/6.25, 10/12.5, 20/12.5, 20/25 mg Tablets.

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

1. Under **Pharmacodynamics**, the following text was added/~~deleted~~:

**Pharmacodynamics**

*Benazepril*

Single and multiple doses of 10 mg or more of benazepril cause inhibition of plasma ACE activity by at least 80%-90% for at least 24 hours after dosing. For up to 4 hours after a 10-mg dose, pressor responses to exogenous angiotensin I were inhibited by 60%-90%. ~~Administration of benazepril to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt and/or volume depleted (see WARNINGS, Hypotension). In single dose studies, benazepril lowered blood pressure within 1 hour, with peak reductions achieved 2-4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple dose studies, once daily doses of 20-80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6-12/4-7 mmHg. The reductions at trough are about 50% of those seen at peak.~~

~~Four dose response studies of benazepril monotherapy using once daily dosing were conducted in 470 mild to moderate hypertensive patients not using diuretics. The minimal effective once daily dose of benazepril was 10 mg; further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10-80 mg). In studies comparing the same daily dose of benazepril given as a single morning dose or as a twice daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.~~

During chronic therapy with benazepril, the maximum reduction in blood pressure with any given dose is generally achieved after 1-2 weeks. The antihypertensive effects of benazepril have continued during therapy for at least 2 years. Abrupt withdrawal of benazepril has not been associated with a rapid increase in blood pressure.

In patients with mild to moderate hypertension, total daily doses of Lotensin 20-40 mg were similar in effectiveness to total daily doses of captopril 50-100 mg, hydrochlorothiazide 25-50 mg, nifedipine SR 40-80 mg, and propranolol 80-160 mg.

The antihypertensive effects of benazepril were not appreciably different in patients receiving high or low sodium diets. In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate. In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

In clinical trials of **benazepril/hydrochlorothiazide** using benazepril doses of 5-20 mg and hydrochlorothiazide doses of 6.25-25 mg, the antihypertensive effects were sustained for at least 24 hours, and they increased with increasing dose of either component. Although benazepril monotherapy is somewhat less effective in blacks than in nonblacks, the efficacy of combination therapy appears to be independent of race.

By blocking the renin-angiotensin-aldosterone axis, administration of benazepril tends to reduce the potassium loss associated with the diuretic. In clinical trials of Lotensin HCT, the average change in serum potassium was near zero in subjects who received 5/6.25 mg or 20/12.5 mg, but the average subject who received 10/12.5 mg or 20/25 mg experienced a mild reduction in serum potassium, similar to that experienced by the average subject receiving the same dose of hydrochlorothiazide monotherapy.

In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

#### *Hydrochlorothiazide*

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

#### *Drug Interactions*

Lotensin HCT potentiates the antihypertensive action of other antihypertensive drugs (e.g. curare derivatives, guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers ACE inhibitors and ARBs and DRIs).

#### Clinical studies

In single-dose studies, benazepril lowered blood pressure within 1 hour, with peak reductions achieved 2-4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple-dose studies, once-daily doses of 20-80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6-12/4-7 mmHg. The reductions at trough are about 50% of those seen at peak.

Four dose-response studies of benazepril monotherapy using once-daily dosing were conducted in 470 mild-to-moderate hypertensive patients not using diuretics. The minimal effective once-daily dose of benazepril was 10 mg; further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10-80 mg). In studies comparing the same daily dose of benazepril given as a single morning dose or as a twice-daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

The antihypertensive effects of benazepril were not appreciably different in patients receiving high- or low-sodium diets.

In clinical trials of **benazepril/hydrochlorothiazide** using benazepril doses of 5-20 mg and hydrochlorothiazide doses of 6.25-25 mg, the antihypertensive effects were sustained for at least 24 hours, and they increased with increasing dose of either component. Although benazepril monotherapy is somewhat less effective in blacks than in nonblacks, the efficacy of combination therapy appears to be independent of race.

2. Under **WARNINGS**, the following text was ~~deleted~~:

#### **Impaired Renal Function**

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

Lotensin HCT should be used with caution in patients with severe renal disease. Thiazides may precipitate azotemia in such patients, and the effects of repeated dosing may be cumulative. When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with ~~severe congestive heart failure~~, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In a small study of hypertensive patients with **unilateral or bilateral renal artery stenosis**, treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. ~~When such patients are treated with Lotensin HCT, renal function should be monitored during the first few weeks of therapy. Some benazepril-treated hypertensive patients with **no apparent preexisting renal vascular disease** have developed increases in blood urea nitrogen and serum creatinine, usually minor~~

and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of Lotensin HCT may be required. **Evaluation of the hypertensive patient should always include assessment of renal function** (see DOSAGE AND ADMINISTRATION).

3. Under **WARNINGS, Fetal Toxicity**, the following text was added:

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension) gestosis (pre-eclampsia), these drugs must not be used to treat hypertension in pregnant women. The use of hydrochlorothiazide for other indications (e.g. heart disease) in pregnancy should be avoided.

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

***Derangements of Serum Electrolytes:*** In clinical trials of benazepril monotherapy, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving benazepril. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia included renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes.

Conversely, treatment with thiazide diuretics has been associated with hypokalemia, hyponatremia, and hypochloremic alkalosis. These disturbances have sometimes been manifest as one or more of dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, and vomiting. Hypokalemia can also sensitize or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH. The opposite effects of benazepril and hydrochlorothiazide on serum potassium will approximately balance each other in many patients, so that no net effect upon serum potassium will be seen. In other patients, one or the other effect may be dominant. Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Chloride deficits are generally mild and require specific treatment only under extraordinary circumstances (e.g., in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients; 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. Calcium excretion is

decreased by thiazides. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland have been observed, with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been seen. Thiazides increase the urinary excretion of magnesium, and hypomagnesemia may result.

### *Serum Electrolyte Abnormalities*

In clinical trials of Lotensin HCT, the average change in serum potassium was near zero in subjects who received 5/6.25 mg or 20/12.5 mg, but the average subject who received 10/12.5 mg or 20/25 mg experienced a mild reduction in serum potassium, similar to that experienced by the average subject receiving the same dose of hydrochlorothiazide monotherapy.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

*Other Metabolic Disturbances:* Thiazide diuretics tend to reduce glucose tolerance and to raise serum levels of cholesterol, triglycerides, and uric acid. These effects are usually minor, but frank gout or overt diabetes may be precipitated in susceptible patients.

### *Hydrochlorothiazide*

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 Lotensin HCT in patients with hypercalcemia.

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

### **Drug Interactions**

#### **Interactions Common for Both Benazepril and Hydrochlorothiazide**

*Potassium Supplements and Potassium-Sparing Diuretics:* As noted above (Derangements of Serum Electrolytes), the net effect of Lotensin HCT may be to elevate a patient's serum potassium, to reduce it, or to leave it unchanged. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently. Concomitant use with Lotensin HCT may effect potassium levels. Monitor potassium periodically.

**Lithium:** Renal clearance of lithium is reduced by thiazides and increase the risk of lithium toxicity. Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Because renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity is presumably raised further when, as in therapy with Lotensin HCT, a thiazide diuretic is coadministered with the ACE inhibitor. Lotensin HCT and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. Monitor lithium levels when used concomitantly with Lotensin HCT.

### **Benazepril**

**Other:** Benazepril has been used concomitantly with beta-adrenergic blocking agents, calcium blocking agents, cimetidine, diuretics, digoxin, and hydralazine without evidence of clinically important adverse interactions. Other ACE inhibitors have had less than additive effects with beta-adrenergic blockers, presumably because drugs of both classes lower blood pressure by inhibiting parts of the renin-angiotensin system. Interaction studies with warfarin and acenocoumarol have failed to identify any clinically important effects of benazepril on the serum concentrations or clinical effects of these anticoagulants.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazides may decrease arterial responsiveness to norepinephrine, but not enough to preclude effectiveness of the pressor agent for therapeutic use. Thiazides may increase the responsiveness to tubocurarine.

The diuretic, natriuretic, and antihypertensive effects of thiazide diuretics may be reduced by concurrent administration of nonsteroidal anti-inflammatory agents.

Cholestyramine and colestipol 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.

### **Hydrochlorothiazide**

Ion exchange resins: 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. 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.

**Digitalis glycosides:** Thiazide-induced hypokalemia or hypomagnesemia may predispose the patients to digoxin toxicity

**Skeletal muscle relaxants:** Possible increased responsiveness to muscle relaxants such as curare derivatives.

**Antidiabetic agents:** Dosage adjustment of antidiabetic drug may be required.

**Antineoplastic agents** (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

**Drugs that alter gastrointestinal motility**: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.

**Cyclosporin**: Concomitant treatment with diuretics may increase the risk of hyperuricaemia and gout-type complications.

**Alcohol, barbiturates or narcotics**: Concomitant administration of thiazide diuretics with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.

**Pressor amines**: Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline but the clinical significance of this effect is not sufficient to preclude their use.

6. Under **Non-clinical safety data/Carcinogenesis, Mutagenicity, Fertility**, the following text was added/deleted:

#### **Fertility**

There are no human fertility data for hydrochlorothiazide. In animal studies, benazepril and hydrochlorothiazide alone or in combination had no effect on fertility and conception (see Non-Clinical Safety Data).

7. Under **Use In Specific Populations**, the following text was added/deleted:

#### **Geriatric Use**

~~Of the total number of patients who received Lotensin HCT in U.S. clinical studies of Lotensin HCT, 19% were 65 or older while about 1.5% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients, and 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. Benazepril and benazeprilat are substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.~~

A limited amount of data suggests that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

#### **Renal Impairment**

Safety and effectiveness of Lotensin HCT in patients with severe renal impairment (CrCL  $\leq$  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.

**Hepatic impairment**

No adjustment of the initial dose is required for patients with mild to moderate hepatic impairment (see Clinical Pharmacology).

**Hydrochlorothiazide**

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

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

~~**Angioedema:** Edema of the lips or face without other manifestations of angioedema (0.3%). See WARNINGS, Angioedema.~~

~~**Cardiovascular:** Hypotension (seen in 0.6% of patients), postural hypotension (0.3%), palpitations, and flushing.~~

~~**Other:** Gout, urinary frequency, arthralgia, myalgia, asthenia, and pain (including chest pain and abdominal pain).~~

~~**Angioedema:** Edema of the lips or face without other manifestations of angioedema. See WARNINGS, Angioedema.~~

~~Monotherapy with **benazepril** has been evaluated for safety in over 6000 patients. In clinical trials, the observed adverse reactions to benazepril were similar to those seen in trials of Lotensin HCT. In post-marketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Another potentially important adverse experience, eosinophilic pneumonitis, has been attributed to other ACE inhibitors.~~

**Post-Marketing Experience**

The following adverse reactions have been identified during post-approval use of either benazepril or hydrochlorothiazide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure:

**Benazepril:** Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia, eosinophilic pneumonitis

~~**Hydrochlorothiazide** has been extensively prescribed for many years, but there has not been enough systematic collection of data to support an estimate of the frequency of the observed adverse reactions. Within organ-system groups, the reported reactions are listed here in decreasing order of severity, without regard~~

to frequency. Unknown frequency: small bowel angioedema, anaphylactoid reactions, hyperkalemia, agranulocytosis, neutropenia.

**Cardiovascular:** Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).

**Metabolic:** Hyperglycemia, glycosuria, and hyperuricemia, pyrexia, asthenia, parathyroid gland changes with hypercalcemia and hypophosphatemia.

### Clinical Laboratory Test Findings

**Serum Electrolytes:** See PRECAUTIONS.

**Creatinine:** Minor reversible increases in serum creatinine were observed in patients with essential hypertension treated with Lotensin HCT. Such increases occurred most frequently in patients with renal artery stenosis (see PRECAUTIONS).

**PBI and Tests of Parathyroid Function:** See PRECAUTIONS.

**Other (Causal Relationships Unknown):** Other clinically important changes in standard laboratory tests were rarely associated with Lotensin HCT administration. Elevations in blood urea nitrogen, uric acid, glucose, SGOT, and SGPT have been reported (see WARNINGS). In the somewhat larger patient population exposed to benazepril monotherapy in U.S. trials, the same abnormalities were reported, together with scattered accounts of hyponatremia, melena, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria.

9. Under **DOSAGE AND ADMINISTRATION**, the following text was added/deleted:

Dose once daily. The dosage may then be increased after 2 to 3 weeks as needed to help achieve blood pressure goals. The maximum recommended dose is 20mg/25mg

**Switch Therapy:** A patient whose blood pressure is not adequately controlled with benazepril alone or with hydrochlorothiazide alone may be switched to combination therapy with Lotensin HCT. The usual recommended starting dose is 10/12.5 mg once daily to control blood pressure.

**Replacement Therapy:** The combination may be substituted for the titrated individual components.

~~Benazepril is an effective treatment of hypertension in once-daily doses of 10-80 mg, while hydrochlorothiazide is effective in doses of 12.5-50 mg per day. In clinical trials of benazepril/hydrochlorothiazide combination therapy using benazepril doses of 5-20 mg and hydrochlorothiazide doses of 6.25-25 mg, the antihypertensive effects increased with increasing dose of either component.~~

The side effects (see WARNINGS) of benazepril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of benazepril and hydrochlorothiazide will be associated with both sets of dose-independent side effects, but regimens in which benazepril is combined with low doses of hydrochlorothiazide produce minimal effects on serum potassium. In clinical trials of Lotensin HCT, the average change in serum potassium was near zero in subjects who received 5/6.25 mg or 20/12.5 mg, but the average subject who received 10/12.5 mg or 20/25 mg experienced a mild reduction in serum potassium, similar to that experienced by the average subject receiving the same dose of hydrochlorothiazide monotherapy.

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.

**Dose Titration Guided by Clinical Effect:** A patient whose blood pressure is not adequately controlled with benazepril monotherapy may be switched to Lotensin HCT 10/12.5 or Lotensin HCT 20/12.5. Further increases of either or both components could depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. Patients whose blood pressures are adequately controlled with 25 mg of daily hydrochlorothiazide, but who experience significant potassium loss with this regimen, may achieve similar blood pressure control without electrolyte disturbance if they are switched to Lotensin HCT 5/6.25. **Replacement**

**Therapy:** The combination may be substituted for the titrated individual components.

**Use in Renal Impairment:** Regimens of therapy with Lotensin HCT need not take account of renal function as long as the patient's creatinine clearance is  $>30 \text{ mL/min/1.73m}^2$  (serum creatinine roughly  $<3 \text{ mg/dL}$  or  $265 \text{ }\mu\text{mol/L}$ ). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Lotensin HCT is not recommended (see WARNINGS).

10. 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, 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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
02/16/2012