DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021468/S-014, S-015

SUPPLEMENT APPROVAL

Shire Pharmaceuticals
Attention: Charles LaPree
Vice President, Global Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19807

Dear Mr. LaPree:

Please refer to your Supplemental New Drug Applications (sNDAs) dated August 17, 2009 (S-014) and December 18, 2009 (S-015), August 17 and December 18, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fosrenol (lanthanum carbonate) 500 mg, 750 mg, and 1000 mg Chewable Tablets.

We acknowledge receipt of your amendment dated October 8 and 29 2010 and February 11, 2011.

The October 29, 2010, submission constituted a complete response to our June 18, 2010, action letter.

These "Prior Approval" supplemental new drug applications provide for labeling revised as follows:

1. In **HIGHLIGHTS/Recent Major Changes**, the following was added:

   Contraindications (4) 2/2011
   Warnings and Precautions, Gastrointestinal adverse Events (5.1) 2/2011

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

   - Bowel obstruction, ileus, and fecal impaction. (4)

3. In **HIGHLIGHTS/WARNING AND PRECAUTIONS**, the following information was added:

   - Serious cases of gastrointestinal obstruction, ileus, and fecal impaction have been associated with lanthanum use, some requiring surgery or hospitalization. Risk factors include constipation and altered gastrointestinal anatomy (2, 5.1)

   - FOSRENOL has radio-opaque properties and therefore may give the appearance typical of an imaging agent during abdominal X-ray procedures. (5.3)

4. In **INDICATIONS AND USAGE**, the first paragraph was changed from:

   FOSRENOL is indicated to reduce serum phosphate in patients with end stage renal disease (ESRD).

To:

FOSRENOL is a phosphate binder indicated to reduce serum phosphate in patients with end stage renal disease (ESRD).

Management of elevated serum phosphorus levels in end stage renal disease patients usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis and reduction of intestinal phosphate absorption with phosphate binders.

5. In **DOSAGE AND ADMINISTRATION**, the section was changed from:

The total daily dose of FOSRENOL® should be divided and taken with meals. The recommended initial total daily dose of FOSRENOL® is 1500 mg. The dose should be titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Serum phosphate levels should be monitored as needed during dose titration and on a regular basis thereafter.

In clinical studies of ESRD patients, FOSRENOL® doses up to 3750 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750 mg/day.

Tablets should be chewed completely before swallowing. To aid in chewing, tablets may be crushed. Intact tablets should not be swallowed.

To:

Divide the daily dose of FOSRENOL and take with or immediately after food**4**. The recommended initial total daily dose of FOSRENOL is 1500 mg. Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached. Monitor serum phosphate levels as needed during dose titration and on a regular basis thereafter.

In clinical studies of ESRD patients, FOSRENOL doses up to 4500 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750 mg/day.

Chew tablets completely before swallowing. To aid in chewing, tablets may be crushed. Do not swallow intact tablets.

Consider potential drug interactions when prescribing FOSRENOL *[see Drug Interactions (7)]*.

6. In **CONTRAINDICATIONS**, the first paragraph was changed from:

None known.

To:

Bowel obstruction, ileus, and fecal impaction.

7. In **WARNINGS AND PRECAUTIONS**, a new section was added:

5.1 Gastrointestinal Adverse Effects

There have been reports of serious cases of gastrointestinal obstruction, ileus, and fecal impaction reported in association with lanthanum, some requiring surgery or hospitalization.

Risk factors for gastrointestinal obstruction identified from post-marketing reports include alteration in gastrointestinal anatomy (e.g., history of gastrointestinal surgery, colon cancer) hypomotility disorders (e.g., constipation, ileus, diabetes) and concomitant medications (e.g., calcium channel blockers). Some cases were reported in patients with no history of gastrointestinal disease.

Advise patients to chew the tablet thoroughly to reduce the risk of adverse gastrointestinal events.

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease, or bowel obstruction were not included in FOSRENOL clinical studies *[see Contraindications (4)]*.

8. In **WARNINGS AND PRECAUTIONS/Diagnostic Tests**, the first paragraph was changed from:

Abdominal x-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent.

To:

FOSRENOL has radio-opaque properties and therefore may give the appearance typical of an imaging agent during abdominal X-ray procedures.

9. In **WARNINGS AND PRECAUTIONS**, the following sections were deleted:

Hepatic Impairment
No studies have been done in patients with hepatic impairment. Although lanthanum is not metabolized, it is excreted in the bile.

Long-term Effects
There were no differences in the rates of fracture or mortality in patients treated with FOSRENOL® compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that FOSRENOL® does not affect the risk of fracture or mortality beyond 3 years.

10. In **ADVERSE REACTIONS**, the following text has been added as the first sentence in the first paragraph:

Overall, the safety profile of FOSRENOL has been studied in over 5200 subjects in completed clinical trials. The most common adverse reactions for FOSRENOL were gastrointestinal events, such as nausea and vomiting and they generally abated over time with continued dosing.

11. In **ADVERSE REACTIONS/Clinical Trials Experience**, the following text has been added as the first sentence in the first paragraph:

    Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

12. In **ADVERSE REACTIONS/Clinical Trials Experience**, the word "reactions" has replaced the word "events" throughout the section.

13. In **ADVERSE REACTIONS/Clinical Trials Experience**, Table 1 has been changed from:

	FOSRENOL % (N=180)	Placebo % (N=95)
Nausea	11	5
Vomiting	9	4
Dialysis graft occlusion	8	1
Abdominal pain	5	o

To:

	FOSRENOL % (N=180)	Placebo % (N=95)
Nausea	11	5
Vomiting	9	4
Abdominal pain	5	0

* expressed a the event rate for each term

14. In **ADVERSE REACTIONS/Clinical Trials Experience**, the following paragraph has been added:

    In an open-label long-term 2 year extension study in 93 patients who had transitioned from other studies, resulting in a total of up to 6 years treatment, mean baseline values and changes in transaminases were similar to those observed in the earlier comparative studies, with little change during treatment.

15. In **ADVERSE REACTIONS/Clinical Trials Experience**, the fourth paragraph, first sentence, the number of patients treated was changed to 944. the paragraph now reads:

    The safety of FOSRENOL was studied in two long-term clinical trials, which included 1215 patients treated with FOSRENOL and 944 with alternative therapy. Fourteen

percent (14%) of patients in these comparative, open-label studies discontinued in the FOSRENOL-treated group due to adverse events. Gastrointestinal adverse reactions, such as nausea, diarrhea and vomiting were the most common types of event leading to discontinuation.

16. In **ADVERSE REACTIONS/Clinical Trials Experience**, Tables 2 and 3 were deleted.

17. In **ADVERSE REACTIONS**, the following text has been added:

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of FOSRENOL: constipation, dyspepsia, allergic skin reactions, hypophosphatemia, and tooth injury.

18. In **DRUG INTERACTIONS**, the following text was added as the first and second paragraphs, respectively:

Lanthanum in FOSRENOL has the potential to bind to drugs with anionic (e.g., carboxyl, carbonyl and hydroxyl) groups. FOSRENOL may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between FOSRENOL and most concomitant drugs. When administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug at least one hour before or three hours after FOSRENOL. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range.

19. In **DRUG INTERACTIONS**, the following section has been added:

7.1 Drugs Binding to Antacids

There is a potential for FOSRENOL to interact with compounds which bind to cationic antacids (i.e. aluminum-, magnesium-, or calcium-based). Therefore, do not take such compounds within 2 hours of dosing with FOSRENOL. Examples of relevant classes of compounds where antacids have been demonstrated to reduce bioavailability include antibiotics (such as quinolones, ampicillin, and tetracyclines), thyroid hormones, ACE-inhibitors, statin lipid regulators, and anti-malarials.

20. In **DRUG INTERACTIONS/Quinolone Antibiotics**, the following text was added as the first paragraph:

Co-administration of FOSRENOL with quinolone antibiotics may reduce the extent of their absorption. The bioavailability of oral ciprofloxacin was decreased by approximately 50% when taken with FOSRENOL in a single dose study in healthy volunteers. Take oral quinolone antibiotics at least 1 hour before or 4 hours after FOSRENOL. When oral quinolones are given for short courses, consider eliminating the doses of FOSRENOL that would be normally scheduled near the time of quinolone intake to improve quinolone absorption *[see Pharmacokinetics (12.3)]***.**

21. In **DRUG INTERACTIONS/Levothyroxine**, the following text was added as the first paragraph:

    The bioavailability of levothyroxine was decreased by approximately 40% when taken together with FOSRENOL. Offset thyroid hormone replacement therapy by 2 hours from dosing with FOSRENOL and monitor thyroid stimulating hormone (TSH) levels *[see Pharmacokinetics (12.3)]*.

22. In **USE IN SPECIFIC POPULATIONS/Pregnancy**, the second paragraph was changed from:

    In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption, increased post-implantation loss, reduced fetal weights, and delayed fetal ossification. Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

    To:

    Studies in pregnant rabbits showed that oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the maximum recommended daily human dose (MRHD) of 5725 mg, on a mg/m2 basis, assuming a 60 kg patient) was associated with increased post-implantation loss, reduced fetal weights, and delayed fetal ossification *[see Nonclinical Toxicology (13.3)]*.

23. In **USE IN SPECIFIC POPULATIONS/Pediatric Use**, the words "The safety and efficacy of FOSRENOL in pediatric patients have not been established", was added as the first sentence of the first paragraph. The paragraph now reads:

    The safety and efficacy of FOSRENOL in pediatric patients have not been established. While growth abnormalities were not identified in long-term animal studies, lanthanum was deposited into developing bone including growth plate. The consequences of such deposition in developing bone in pediatric patients are unknown. Therefore, the use of FOSRENOL in this population is not recommended.

24. In **OVERDOSAGE**, the text in the first paragraph was changed from:

    There is no experience with FOSRENOL® overdosage. Lanthanum carbonate was not acutely toxic in animals by the oral route. No deaths and no adverse effects occurred in mice, rats or dogs after single oral doses of 2000 mg/kg. In clinical trials, daily doses up to 4718 mg/day of lanthanum were well tolerated in healthy adults when administered with food, with the exception of GI symptoms. Given the topical activity of lanthanum in the gut, and the excretion in feces of the majority of the dose, supportive therapy is recommended for overdosage.

To:

The symptoms associated with overdose are adverse reactions such as headache, nausea, and vomiting. In clinical trials, daily doses up to 6000 mg/day of lanthanum carbonate were well tolerated in healthy adults when administered with food, with the exception of GI symptoms. Given the topical activity of lanthanum in the gut, and the excretion in feces of the majority of the dose, supportive therapy is recommended for overdosage. Lanthanum carbonate was not acutely toxic in animals by the oral route. No deaths and no adverse effects occurred in mice, rats or dogs after single oral doses of 2000 mg/kg (1.7, 3.4, and 11.3 times the MRHD, respectively, on a mg/m^2 basis).

25. In **CLINICAL PHARMACOLOGY**, the following text was deleted:

Patients with end stage renal disease (ESRD) can develop hyperphosphatemia that may be associated with secondary hyperparathyroidism and elevated calcium phosphate product. Elevated calcium phosphate product increases the risk of ectopic calcification. Treatment of hyperphosphatemia usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis and inhibition of intestinal phosphate absorption with phosphate binders. FOSRENOL® does not contain calcium or aluminum.

26. In **CLINICAL PHARMACOLOGY/Mechanism of Action**, the following text was added as the first paragraph:

FOSRENOL is a phosphate binder that reduces absorption of phosphate by forming insoluble lanthanum phosphate complexes that pass through the gastrointestinal (GI) tract unabsorbed. Both serum phosphate and calcium phosphate product are reduced as a consequence of the reduced dietary phosphate absorption.

27. In **CLINICAL PHARMACOLOGY/Pharmacodynamics**, the first and second paragraphs have been changed from:

Lanthanum carbonate dissociates in the acid environment of the upper GI tract to release lanthanum ions that bind dietary phosphate released from food during digestion. FOSRENOL® inhibits absorption of phosphate by forming highly insoluble lanthanum phosphate complexes, consequently reducing both serum phosphate and calcium phosphate product.

In vitro studies have shown that in the physiologically relevant pH range of 3 to 5 in gastric fluid, lanthanum binds approximately 97% of the available phosphate when lanthanum is present in a two-fold molar excess to phosphate. In order to bind dietary phosphate efficiently, lanthanum should be administered with or immediately after a meal.

To:

In vitro studies have shown that lanthanum effectively binds phosphate in the physiologically relevant pH range of 3 to 7. In simulated gastric fluid, lanthanum binds approximately 97% of the available phosphate at pH 3-5 and 67% at pH 7, when lanthanum is present in a two-fold molar excess to phosphate. Bile acids have not been

shown to affect the phosphate binding affinity of lanthanum. In order to bind dietary phosphate efficiently, FOSRENOL must be administered with or immediately after food.

In five Phase I pharmacodynamic studies comparing the reduction from baseline of urinary phosphorus excretion in healthy volunteers (N=143 taking lanthanum carbonate), it was shown that the mean intestinal phosphate binding capacity of lanthanum ranged from 235 – 468 mg phosphorus/day when lanthanum was administered at a dose of 3 g per day with food. By comparison, in one study with an untreated control group (n=10) and another study with a placebo group (n=3), the corresponding mean changes from baseline were 3 mg phosphorus/day and 87 mg phosphorus/day, respectively.

28. In **CLINICAL PHARMACOLOGY/Pharmacokinetic**s, the text "The effect of food on the bioavailability of FOSRENOL® has not been evaluated", has been deleted from the first paragraph.

29. In **CLINICAL PHARMACOLOGY/Pharmacokinetics/Absorption and Distribution**, the following text has been added to the third paragraph:

    In animal studies, lanthanum concentrations in several tissues, particularly gastrointestinal tract, mesenteric lymph nodes, bone, and liver, increased over time to levels several orders of magnitude higher than those in plasma. The level of lanthanum in the liver was higher in renally impaired rats due to higher intestinal absorption. Lanthanum was found in the lysosomes and the biliary canal consistent with transcellular transport. Steady state tissue concentrations in bone and liver were achieved in dogs between 4 and 26 weeks. Relatively high levels of lanthanum remained in these tissues for longer than 6 months after cessation of dosing in dogs. There is no evidence from animal studies that lanthanum crosses the blood-brain barrier.

30. In **CLINICAL PHARMACOLOGY/Pharmacokinetics/Metabolism and Elimination**, the first paragraph was changed from:

    Lanthanum is not metabolized and is not a substrate of CYP450. *In vitro* metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40 µg/ml does not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, and 3A4/5). Lanthanum was cleared from plasma following discontinuation of therapy with an elimination half-life 53 hours.

    To:

    Lanthanum is not metabolized. Lanthanum was cleared from plasma of patients undergoing dialysis with an elimination half-life of 53 hours following discontinuation of therapy.

31. In **CLINICAL PHARMACOLOGY/Pharmacokinetics/Drug Interactions**, the following text was deleted:

    In Vitro- Drug Interaction **- Gastric Fluid:** The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, and enalapril) was investigated in

simulated gastric fluid. The results suggest that precipitation in the stomach of insoluble complexes of these drugs with lanthanum is unlikely.

In Vivo- Drug Interactions:
Lanthanum carbonate is neither a substrate nor an inhibitor of CYP450 enzymes. The absorption of a single dose of 1000 mg of FOSRENOL® is unaffected by co-administration of citrate. No effects of lanthanum were found on the absorption of digoxin (0.5 mg), metoprolol (100 mg), or warfarin (10 mg) in healthy subjects co-administered lanthanum carbonate (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of co-administration). Potential pharmacodynamic interactions between lanthanum and these drugs (e.g., bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies were done with the maximum recommended therapeutic dose of lanthanum carbonate. No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

32. In **CLINICAL PHARMACOLOGY/Pharmacokinetics/***Drug Interactions*, the following text was added:

FOSRENOL has a low potential for systemic drug-drug interactions because of the very low bioavailability of lanthanum and because it is not a substrate or inhibitor of major cytochrome P450 enzyme groups involved in drug metabolism (CYP1A2, CYP2C9/10, CYP2C19, CYP2D6, and CYP3A4/5).

FOSRENOL does not alter gastric pH. Therefore, FOSRENOL drug interactions based on altered gastric pH are not expected.

In an *in vitro* investigation, lanthanum did not form insoluble complexes when mixed in simulated gastric fluid with warfarin, digoxin furosemide, phenytoin, metoprolol, and enalapril. Clinical studies have shown that FOSRENOL (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of co-administration) administered 30 minutes earlier did not alter the pharmacokinetics of oral warfarin (10 mg), digoxin (0.5 mg), or metoprolol (100 mg). Potential pharmacodynamic interactions between lanthanum and these drugs (e.g., bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies were done with the maximum recommended therapeutic dose of lanthanum carbonate. No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

Ciprofloxacin
In a randomized, two–way crossover study in healthy volunteers examining the interaction potential of a single oral dose of ciprofloxacin (750 mg) alone and with lanthanum carbonate (1 g TID), the maximum plasma concentration of ciprofloxacin was reduced by 56% and the area under the ciprofloxacin plasma concentration-time curve was reduced by 54%. The 24-h urinary recovery of ciprofloxacin was reduced 52% by FOSRENOL *[see Drug Interactions (7.2)]***.**

Levothyroxine

In a single-dose crossover study of levothyroxine (1 mg) with or without simultaneous administration of a single dose of FOSRENOL (500 mg) in six euthyroid normal healthy

volunteers, the area under the serum T4 concentration-time curve was decreased by 40% *[see Drug Interactions (7.3)]***.**

Fat Soluble Vitamins

FOSRENOL appears not to affect the availability of fat soluble vitamins (A, D, E, and K) or other nutrients *[see Clinical Studies (14.2)]***.**

Citrate

Citrate did not increase the absorption of lanthanum.

33. In **NON CLINICAL TOXICOLOGY/Carcinogenesis, Mutagenesis, Impairment of Fertility**, "maximum human dose" was deleted from the first paragraph. The paragraph now reads:

Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg of the salt per kg/day [2.5 times the MRHD of 5725 mg, on a mg/m^2 basis, assuming a 60-kg patient] revealed no evidence of carcinogenic potential. In the mouse, oral administration of lanthanum carbonate for up to 99 weeks, at a dose of 1500 mg/kg/day (1.3 times the MRHD) was associated with an increased incidence of glandular stomach adenomas in male mice.

34. In **NON CLINICAL TOXICOLOGY**, the following section has been added:

13.3 Developmental toxicity

In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption, increased post-implantation loss, reduced fetal weights, and delayed fetal ossification. Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

35. In **PATIENT COUNSELING INFORMATION**, the first paragraph was changed from:

FOSRENOL® tablets should be taken with or immediately after meals. Tablets should be chewed completely before swallowing. **To aid in chewing, tablets may be crushed.** Intact tablets should not be swallowed.

To:

Advise patients to take FOSRENOL tablets with or immediately after food, and to chew or to crush tablets completely before swallowing.

Advise patients who are taking an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after FOSRENOL.

Notify your physician that you are taking FOSRENOL prior to an abdominal x-ray *[see Warnings and Precautions (5.3)]*.

36. In **PATIENT COUNSELING INFORMATION**, manufacturing information has been added:

    Manufactured by DSM Pharmaceuticals Inc.
    5900 NW Greenville Blvd,
    Greenville, NC 27834

37. The revision date and version number have been updated.

There are no other changes from the last approved package insert from May 20, 2009.

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

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
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
04/27/2011