DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021468/S-016

SUPPLEMENT APPROVAL

Shire Development, Inc.
Attention: Zohra Lomri
Associate Director, Global Regulatory Affairs
725 Chesterbrook Boulevard
Wayne, PA 19087

Dear Ms. Lomri:

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 Fosrenol (lanthanum carbonate) 500 mg, 750 mg, and 1000 mg Chewable Tablets.

We acknowledge receipt of your amendment dated August 25, 2011.

This "Prior Approval" supplemental new drug application provides for the addition of a Medication Guide, Dear Healthcare Provider Letter; Carton and Container Labels, and Labeling revised as follows:

For Labeling:

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

   Dosage and Administration (2) 08/2011

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the following bullets were added:

   - **Chew or crush tablets completely before swallowing. Do not swallow intact tablets**. **Consider crushing tablets completely for patients with poor dentition. (2)**
   - Divide the total daily dose of FOSRENOL. (2)

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

   - Advise patients to chew or crush the tablet completely to reduce the risk of serious adverse gastrointestinal events. (5.1)

4. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following bullet was changed from:

   - 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)

To:

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

5. In **HIGHLIGHTS/ADVERSE REACTIONS**, the first bullet was changed from:

   - The most common Gastrointestinal adverse reactions included, nausea, vomiting, diarrhea, and abdominal pain. (6.1)

To:

   - Gastrointestinal adverse reactions, such as nausea, diarrhea, abdominal pain, and vomiting were the most common types of events leading to discontinuation. (6.1)

6. Under **DOSAGE AND ADMINISTRATION**, the word "total" was added to the first sentence of the first paragraph, and the word "meals" replaces the word "food". The paragraph now reads:

   Divide the total daily dose of FOSRENOL and take with or immediately after meals. 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.

7. Under **DOSAGE AND ADMINISTRATION**, the third paragraph was changed from:

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

To:

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

   Consider crushing tablets completely for patients with poor dentition.

8. Under **WARNINGS AND PRECAUTIONS**, the third paragraph was changed from:

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

To:

   Advise patients to chew the tablet completely to reduce the risk of serious adverse gastrointestinal events such as those described above.

9. Under **ADVERSE REACTIONS**, the words "and abdominal pain" were added to the section. The section now reads:

   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 vomiting, and abdominal pain and they generally abated over time with continued dosing.

10. Under **ADVERSE REACTIONS/Clinical Trials**, the words "clinical trials" replaced the word "studies" in the fourth paragraph.

11. Under **ADVERSE REACTIONS/Clinical Trials**, the following was added as the fifth paragraph:

    In pooled active comparator controlled clinical trials, hypocalcemia was noted with an incidence of approximately 5% in both lanthanum and active comparator groups. A nonclinical study and a phase 1 study have shown reduced absorption of calcium in the intestine with lanthanum carbonate treatment.

12. In **USE IN SPECIFIC POPULATIONS/Labor and Delivery**, the word "FOSRENOL" replaced the words "lanthanum carbonate".

13. In **OVERDOSAGE**, the first paragraph was changed from:

    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).

    The symptoms associated with overdose are adverse reactions such as headache, nausea and vomiting. In clinical trials in healthy adults, GI symptoms were reported with daily doses up to 6000 mg/day of lanthanum carbonate administered with food. 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).

14. Under **DESCRIPTION**, the inactive ingredients were alphabetized. They now read:

    Each FOSRENOL, white to off-white, chewable tablet contains lanthanum carbonate hydrate equivalent to 500, 750, or 1000 mg of elemental lanthanum and the following inactive ingredients: colloidal silicon dioxide NF, dextrates (hydrated) NF, magnesium stearate NF.

15. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics**, the word "effectively" was deleted from the first and the third sentence of the first paragraph. The word "food" was replaced with the word "meals" in the fourth sentence.

16. Under **HOW SUPPLIED/STORAGE AND HANDLING**, the word "debossed" replaces the word "embossed" in the second sentence.

17. Under **PATIENT COUNSELING INFORMATION**, the section was changed from:

> Advise patients to take FOSRENOL tablets with or immediately after food. **Chew or 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 separate the dosing of FOSRENOL from the affected drug by several hours. *[see Drug Interactions (7)]*.
>
> Notify your physician that you are taking FOSRENOL prior to an abdominal x-ray *[see Warnings and Precautions (5.2)]*.

To:

> Advise patients to take FOSRENOL tablets with or immediately after meals. **Instruct patients to chew or crush tablets completely before swallowing**. It should be emphasized that FOSRENOL tablets should not be swallowed intact. Consider crushing tablets completely for patients with poor dentition *[see Dosage and Administration (2)]*.
>
> 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 separate the dosing of FOSRENOL from the dosing of the affected drug by several hours *[see Drug Interactions (7)]*.
>
> Advise patients to notify their physician that they are taking FOSRENOL prior to an abdominal x-ray *[see Warnings and Precautions (5.2)]*.

18. The revision date and version number were updated.

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

For All Trade Container Labels – 500 mg, 750 mg, and 1000 mg

1. The medication guide statement to comply with 21 CFR 208.24: "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide" was added.

2. The prominence of the net quantity statement was decreased and relocated to the bottom of principal display panel.

3. The 'Rx Only' statement was unbolded and relocated to the bottom of principal display panel.
4. The prominence of the presentation of the following statements was increased and the statements were relocated to the middle of the principal display panel:

> Do not swallow tablets whole.
> Chew or crush tablets completely before swallowing.

Take with or immediately after food.

For All Trade Carton Labeling - 500 mg, 750 mg, and 1000 mg

5. The prominence of the net quantity statement was decreased and relocated to the bottom of principal display panel.

6. The 'Rx Only' statement was unbolded on all carton display panels.

7. On the top carton flap, the quantity and 'Rx Only' statements were removed and replaced with the following statements:

   Do not swallow tablets whole.
   Chew or crush tablets completely before swallowing.
   Take with or immediately after food.

8. The prominence of the presentation of the following statements was increased:

   Do not swallow tablets whole.
   Chew or crush tablets completely before swallowing.
   Take with or immediately after food.

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, Medication Guide), 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 021468/S-016**" Approval of this submission by FDA is not required before the labeling is used.

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
(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

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
Medication Guide
Dear Healthcare Provider Letter

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
09/02/2011