DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021468/S-020
NDA 204734/S-001

SUPPLEMENT APPROVAL

Shire Development LLC
Attention: Jiao Wei
Manager, Global Regulatory Affairs
300 Shire Way
Lexington, MA 02421

Dear Ms. Wei:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 23, 2015, 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 (NDA 021468) and 750 mg and 1000 mg Oral Powder (NDA 204734).

We also refer to your amendment dated February 17, 2016.

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

The following changes were made to the Package Insert:

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

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2)	02/2016
Warnings and Precautions (5.1)	02/2016

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the following text was added to the end of the fourth bullet:

- FOSRENOL Oral Powder: Sprinkle powder on a small quantity of applesauce or other similar food and consume immediately. Consider powder formulation in patients with poor dentition, or who have difficulty chewing tablets (2)

3. Under **DOSAGE AND ADMINISTRATION**, the following text was added to the end of the 7th paragraph:

Consider using the oral powder formulation in patients with poor dentition or who have difficulty chewing tablets

4. Under **WARNINGS AND PRECAUTIONS**, The following text was added/deleted:

~~There have been reports of s~~Serious cases of gastrointestinal obstruction, ileus, subileus, gastrointestinal perforation and fecal impaction have been reported in patients taking ~~association with~~ lanthanum, some requiring surgery or hospitalization.

Risk factors for gastrointestinal obstruction and gastrointestinal perforation identified from post-marketing reports in patients taking FOSRENOL Chewable Tablets include altered gastrointestinal anatomy (e.g., diverticular disease, peritonitis, history of gastrointestinal surgery, gastrointestinal colon cancer, gastrointestinal ulceration), hypomotility disorders (e.g., constipation, ileus, subileus, diabetic gastroparesis) and concomitant medications (e.g., calcium channel blockers). Some cases were reported in patients with no history of gastrointestinal disease.

~~Advise patients who are prescribed FOSRENOL Chewable Tablets to chew the tablet completely to reduce the risk of serious adverse gastrointestinal events such as those described above.~~

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

Advise patients who are prescribed FOSRENOL Chewable Tablets to chew the tablet completely to reduce the risk of serious adverse gastrointestinal events such as those described above.

5. Under **ADVERSE REACTIONS**, the following text was added:

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Gastrointestinal Adverse Effects *[see Warnings and Precautions (5.1)]*

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of FOSRENOL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: constipation, intestinal perforation, intestinal obstruction, ileus, subileus, dyspepsia, allergic skin reactions, hypophosphatemia, and tooth injury while chewing the tablet.

6. Under **PATIENT COUNSELING INFORMATION**, the following text was added to the 5th and 8th paragraphs:

Instruct patients who are prescribed FOSRENOL Chewable Tablets to chew or crush tablets completely before swallowing. Emphasize that FOSRENOL Chewable

Tablets should not be swallowed intact. Consider crushing FOSRENOL Chewable Tablets completely or prescribing the oral powder formulation for patients with poor dentition or who have difficulty chewing tablets *[see Dosage and Administration (2)]*.

Advise patients to notify their physician that they are taking FOSRENOL prior to an abdominal X-ray or if they have a history of gastrointestinal disease *[see Warnings and Precautions (5.1,5.2)]*.

7. The manufacturing facility address was updated to:

Manufactured for Shire US Inc., 300 Shire Way, Lexington, MA 02421~~Wayne, PA 19087.~~
FOSRENOL is a trademark of Shire LLC.

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

The following changes were made to the Medication Guide:

1. Under **What is the most important information I should know about FOSRENOL?,** the following text was added/deleted:

FOSRENOL may cause a bowel blockage, a hole in the bowel or severe constipation, which can be serious, and sometimes lead to surgery or treatment in a hospital.

- You may have a higher risk of bowel blockage, a hole in the bowel or severe constipation if you take FOSRENOL and have:
- a history of ~~bowel~~ surgery, ulcers or ~~colon~~ cancer in the stomach or bowel
- a history of bowel blockage, or problems resulting in a decreased movement of food through your stomach and bowel (e.g. feeling full quickly after eating or constipation)~~decreased movement of your bowel, constipation, or diabetes~~
- an infection or inflammation of the stomach/bowel (peritonitis)

2. Under **FOSRENOL may not be right for you. Before starting FOSRENOL, tell your healthcare provider if you:**

- have a history of ~~bowel~~ surgery, ulcers or ~~colon~~ cancer in the stomach or bowel
- have a history of a bowel blockage, constipation, or problems resulting in a decreased movement of food through your stomach and bowel especially if you also have diabetes~~ileus or constipation, or diabetes~~
- have ~~stomach ulcers~~, ulcerative colitis, ~~or~~ Crohn's disease or an infection or inflammation of the stomach/bowel (peritonitis)
- plan to have an X-ray of your stomach (abdomen)
- have any other medical conditions
- are pregnant, plan to become pregnant, or plan to breastfeed. It is not known if FOSRENOL will harm your unborn baby

3. The revision date was updated.

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
02/24/2016