DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Angus Russell
Chief Executive Officer
Shire Development Inc.
725 Chesterbrook Blvd
Wayne, PA 19087-5637

RE: NDA# 21-468
Fosrenol® (lanthanum carbonate hydrate) Chewable Tablets
MACMIS # 17999

WARNING LETTER

Dear Mr. Russell:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the "HOW I STAY ON TRACK" brochure (FOS-00243) (brochure) included in the On track-Binder (FOS-00043) (binder) for Fosrenol® (lanthanum carbonate hydrate) Chewable Tablets (Fosrenol) submitted under cover of Form FDA-2253 by Shire Development Inc. (Shire). The brochure is false or misleading because it omits risk information associated with Fosrenol, makes unsubstantiated superiority claims, and overstates the efficacy and broadens the indication of Fosrenol. Thus, the brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (ii).

Background

The INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Fosrenol states:

> FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease.

Fosrenol is associated with numerous risks and precautions. The PI contains precautions regarding use in patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction. In addition, the duration of treatment exposure and time of observation in the clinical program were too short to conclude that Fosrenol does not affect the risk of fracture or mortality beyond three years. Furthermore, the effect of Fosrenol on the absorption of vitamins and other nutrients has not been studied in pregnant women. Fosrenol is not recommended for use during pregnancy. The use of Fosrenol in pediatric patients is also not

recommended because, while growth abnormalities were not identified in long-term animal studies, lanthanum was deposited into developing bone including growth plate.

The ADVERSE REACTIONS section of the PI presents the following adverse events as occurring more frequently (≥ 5% difference) in the Fosrenol group than placebo: nausea (11% vs. 5%), vomiting (9% vs. 4%), dialysis graft occlusion (8% vs. 1%), and abdominal pain (5% vs. 0%). Fourteen percent of patients in two comparative, open-label studies discontinued Fosrenol therapy due to adverse events.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested by the materials. The brochure makes the following efficacy claims for Fosrenol:

- "FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease"
- "Your doctor has prescribed FOSRENOL® (lanthanum carbonate) to help remove phosphorus from your blood."
- "FOSRENOL is a phosphate binder that begins working in the stomach. FOSRENOL works like a sponge to soak up phosphorus."
- "What you can do about high phosphorus: …. Always take your FOSRENOL as directed by your doctor"

However, the brochure fails to communicate **any** of the risk information associated with Fosrenol, including the numerous precautions and adverse reactions listed in the Background section above. We note that this brochure is intended for patients who have already received a prescription for Fosrenol; however, this does not mitigate the need to communicate important information to the patient regarding precautions and potential adverse reactions for Fosrenol.

We note that the brochure includes the statement, "*Please see accompanying Full Prescribing Information*" (emphasis in original) in small type on the bottom of the back cover. We also note that a separate "Important Safety Information" sheet and a PI are included in the back part of the binder. However, this does not mitigate the complete omission of risk information from the brochure itself.

DDMAC had previously objected, in an untitled letter dated May 1, 2008, to the dissemination of a Notebook (FOS1598) and a Medical Exam Light Case (FOS1597) for Fosrenol that failed to include any risk information as well as the drug product's indication and other material contextual information. We are concerned that you are continuing to promote Fosrenol in a similarly violative manner.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The brochure includes the following claims:

- "FOSRENOL is a phosphate binder that begins working in the stomach. FOSRENOL works like a sponge to soak up phosphorus. . . . Other binders don't begin working until farther into your digestive system, after most of the phosphorous has already been absorbed" (page 4).

These claims are presented in conjunction with a large picture of a sponge. The totality of this presentation implies that Fosrenol is more effective than other phosphate binders because it works earlier in the digestive system (i.e., the stomach) than these other binders and therefore binds more phosphorus. FDA is not aware of **any** substantial evidence or substantial clinical experience to support the implication that Fosrenol is superior to other phosphate binders in reducing serum phosphate levels. Generally, claims of superiority must be supported by two adequate and well-designed, head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug. In addition, we are not aware of support for the implication that Fosrenol's phosphorus binding action occurs earlier than that of any other phosphorus binder. If you have data to support these claims, please submit them to FDA for review.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. Pages 3 and 4 of the brochure contain the following claims (emphasis in original):

- "You may not feel it, but having too much phosphorous in your blood is serious. It can lead to:
    - *Mineral deposits in tissues found in your heart, blood vessels, eyes, joint and skin*
    - *Bone disease*
    - *Heart disease or death*."

- "FOSRENOL works like a sponge to soak up phosphorus."

While hyperphosphatemia can lead to negative outcomes as described above, and the presentation excerpted above does not directly assert that Fosrenol will correct the negative outcomes associated with hyperphosphatemia, the implication created by placing this presentation in a piece promoting Fosrenol for the treatment of hyperphosphatemia is that Fosrenol can help prevent the listed consequences of hyperphosphatemia, including the calcification of vascular and nonvascular tissues, bone disease, heart disease and death. While Fosrenol has been shown to reduce serum phosphate levels in end stage renal

disease patients, we are not aware of substantial evidence or substantial clinical experience demonstrating the effect of treatment with Fosrenol on prevention of mineral deposition, bone disease, heart disease, or death. If you do, in fact, have data to support these claims, you should submit them to FDA for review.

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. The brochure speaks in broad terms about Fosrenol's use in treating hyperphosphatemia and thereby implies it is appropriate for all patients who suffer from this condition. For example, the following statements appear on page 2 of the brochure: "Your doctor has prescribed FOSRENOL® (lanthanum carbonate) to help remove phosphorous from your blood. Too much phosphorous in the blood is called hyperphosphatemia." Similarly, the presentation on page 4 of the brochure underneath the "Why Choose FOSRENOL®" headline discusses how "FOSRENOL works like a sponge to soak up phosphorus." In addition, the presentation on page 5 of the brochure indicates that the things one can "do about high phosphorus" include "always tak[ing] your FOSRENOL as directed by your doctor." The totality of these claims and presentations suggest that Fosrenol therapy is generally appropriate for any patient who has hyperphosphatemia. However, Fosrenol is only indicated to reduce serum phosphate **in patients with end stage renal disease**. We note that the presentation on page 5 of the brochure also indicates that patients should "Go to every dialysis appointment…"; however, this reference to dialysis is not sufficient to communicate that Fosrenol is only approved to treat patients with end stage renal disease. We also note that the back cover of the brochure includes the statement, "FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease," in small type at the bottom of the page; however, this inconspicuous statement on the back cover of the brochure is not sufficient to mitigate the misleading impression communicated by the totality of the other presentations in the brochure that Fosrenol is appropriate for any patient with hyperphosphatemia. Thus, the brochure misleadingly broadens the indication for Fosrenol.

Conclusion and Requested Action

For the reasons discussed above, the binder misbrands Fosrenol in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (ii).

DDMAC requests that Shire immediately cease the dissemination of violative promotional materials for Fosrenol such as those described above. Please submit a written response to this letter on or before November 20, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Fosrenol that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are repeated, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the 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, or facsimile at 301-847-8444. In all future

correspondence regarding this matter, please refer to MACMIS 17999 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Fosrenol comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21468	ORIG-1	SHIRE DEVELOPMENT INC	FOSRENOL(LANTHANUM CARBONATE HYDRATE)

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

/s/

THOMAS W ABRAMS
11/05/2009