DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Dennis Ahern, MS
Associate Director, Regulatory Affairs
Shire Development, Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

RE: NDA # 21-468
Fosrenol® (lanthanum carbonate)
MACMIS ID # 16359

Dear Mr. Ahern:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a Notebook (FOS1598) and a Medical Exam Light Case (FOS1597) submitted under cover of Form FDA-2253 by Shire Development, Inc. (Shire) for Fosrenol® (lanthanum carbonate) (Fosrenol). These pieces are violative because although they have the form of reminder labeling, which is exempted by regulation from the requirements under the Federal Food, Drug, and Cosmetic Act (Act) for the disclosure of risk and other information, for the reasons set forth below, we have determined that your promotional materials are not appropriate reminder labeling. Therefore, the pieces misbrand Fosrenol in violation of the Act, 21 U.S.C. 352(f)(1), 352(a), & 321(n) and FDA's implementing regulations, 21 CFR 201.100(f) & 1.21, as they fail to include, among other things, the drug product's indication as well as material contextual information and information addressing the risks associated with Fosrenol.

Background

The INDICATIONS AND USAGE section of the 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. For example, 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. While growth abnormalities were not identified in

long-term animal studies, lanthanum was deposited into developing bone including growth plate. Therefore, the use of Fosrenol in pediatric patients is not recommended. Finally, 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 Material Facts

According to FDA regulations, reminder labeling is labeling that calls attention to the name of the drug product, but does not include its indication, dosage recommendations, or other representations or suggestions relating to the drug product. See 21 CFR 201.100(f). Although the promotional materials cited above do not state the drug product's indication, the claims presented on the materials nevertheless make representations or suggestions about Fosrenol.

Specifically, the notebook and medical exam light case present the claims, "First line," "For reductions that last," and "Calcium-Free." The combination of the claims with the Fosrenol logo that is imprinted on the promotional materials makes several suggestions regarding Fosrenol therapy. The claim "First line" suggests that Fosrenol is the treatment of choice for the product's approved indication. The claim "For reductions that last" suggests the reductions provided by Fosrenol last for a long period of time. Finally, the claim, "Calcium-Free," suggests that Fosrenol may be useful in a patient population that may benefit from limited exogenous calcium intake. Reminder pieces may not include, among other things, representations or suggestions concerning effectiveness or patient population. Because the materials make such representations or suggestions, the pieces cited above are not considered reminder labeling and appropriate indication and risk information need to be included. However, these pieces fail to include this information. We also note that the claim "For reductions that last" omits material contextual information. While there is data in the PI regarding maintenance of reduction for up to 3 years, this data is from open-label extension trials that only included a small subset of patients (n=161), forty-six of whom actually received continuous Fosrenol treatment for a total of three years. This claim fails to reveal these important limitations to the long-term data available on maintenance of reduction.

Conclusion and Requested Action

For the reasons discussed above, the promotional materials misbrand Fosrenol under the Act, 21 U.S.C. 352(f) (1), 352(a), & 321(n) and FDA's implementing regulations. 21 CFR 201.100(f) & 1.21.

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 May 16, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Fosrenol such as those described above, and explaining your plan for discontinuing use of such 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID # 16359 in addition to the NDA number. We remind you that only written communications are considered official.

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.

Sincerely,

{See appended electronic signature page}

Lisa M. Hubbard, R.Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Lisa Hubbard

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