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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-468

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-468

Shire Pharmaceutical Development, Inc.
Attention: Rick Lilley, Ph.D.
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Lilley:

Please refer to your new drug application (NDA) dated April 30, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) 250 and 500 mg Chewable Tablets.

We acknowledge receipt of your submissions dated May 21 and 22, June 7, 14, 19 and 28, July 11, 25 and 30, August 5, 14, 27 (two), 29 and 30 (three), September 10, 13, 16, 18 and 25, October 3, 8, 22, 24 and 28, November 1, 4, 11, 15, 21, 22 (two), 27 (two) and 29, December 13 (two), 16, 18, 20 (two), 23, 2002 and January 23, 27 and 28, and February 12, 2003.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies:

CLINICAL
While it is clear that lanthanum carbonate is effective as a phosphate binder in patients with end-stage renal disease (ESRD), there has been insufficient evaluation of lanthanum carbonate's safety.

1. Adverse Events Leading to Discontinuation
It is clear that the rate of discontinuation for adverse events (especially gastrointestinal adverse events) was significantly higher for patients receiving lanthanum compared with standard phosphate binders over all periods of exposure in the clinical trials. Insufficient information is available regarding the resolution of these symptoms following lanthanum discontinuation. While in most cases such symptoms would be expected to resolve when a study drug is discontinued, given the high concentration of lanthanum in the GI tract following oral administration and the uncertainties about the rate of elimination of lanthanum in patients with ESRD, our concern is that these symptoms may not resolve quickly, presenting a real risk of malnutrition and additional injury in this population.

Resolution of this clinical issue will require data regarding the timing and extent of resolution of reported serious adverse events (especially events leading to discontinuation) in patients receiving lanthanum in the long term trials.

2. Long Term Safety Information

It is clear from the bone histologic examination that lanthanum is absorbed following oral administration and is then deposited in tissue. It is deposited widely in animals, including the GI tract, bone and cardiac tissues in patients with ESRD. There is less information available, but bone deposition has been clearly demonstrated. As we do not yet know if (or when) a steady-state tissue concentration of lanthanum should be expected following chronic use, it is difficult to use the present database to assess the possibility of significant long-term toxicities resulting from tissue deposition of lanthanum. Given the history of significant, but unpredicted, long-term bone toxicity following the use of aluminum containing antacids, where toxicity was not manifest clinically for several years after initial exposure, the current database is inadequate with respect to long-term follow-up to exclude significant toxicity, including bone toxicity.

Additional long-term data will therefore be needed. Deciding on the extent and duration of long-term safety data will require additional data on the rate at which lanthanum continues to be deposited during chronic administration of lanthanum to patients with ESRD. These data will provide a basis for discussions of how to assess the long term safety of lanthanum.

3. Prolongation of the QT Interval on the Surface Electrocardiogram

Lanthanum appears to prolong the QT interval by a mean of 5-10 milliseconds when compared with the other phosphate binders, as shown in the LAM-IV-307 study. This effect is poorly characterized in the available trial data and additional clinical data are needed on the following:

1. Time-course of the effects of lanthanum on QT interval, including time to resolution following drug discontinuation.
2. Assessment of link between QT prolongation and risk of cardiac death in patients with ESRD. Such an assessment may be done using the available and pending data from the long-term clinical trials.

BIOPHARMACEUTICS

The following deficiencies related to the clinical pharmacology of lanthanum have been identified.

1. Absorption, Distribution, Metabolism and Elimination

While it is clear that lanthanum is absorbed from the GI tract and is deposited in many tissues, additional information on the following are needed:

a. The time-course of lanthanum absorption, metabolism and elimination, including information on when a steady-state tissue concentration of lanthanum should be expected following chronic use.

b. The amount of lanthanum that is absorbed from the GI tract, and what factors (in particular the effects of dietary changes and renal or hepatic impairment) that can modify lanthanum absorption, tissue deposition and elimination.

2. Dissolution

Method: The originally proposed dissolution method for the crushed tablets (USP Apparatus 2, [redacted] rpm, [redacted]) is acceptable on an interim basis. We understand, however, that you will continue to work to develop a better dissolution methodology for the whole tablets. Within one year from the date of this letter you should submit a final report describing the development and validation of this method for the whole tablets, including complete dissolution data for at least [redacted] lots of the 250 and 500 mg tablets (at least 12 units/lot) using the revised method.

Specification: The originally proposed dissolution specification of Q = — % at [ ] is not acceptable. The provided dissolution data for several clinical and stability lots using crushed tablets showed that a specification of [ ] would be more appropriate for both the 250 and 500 mg Fosrenol chewable tablets.

3. Approval of the 500 mg Tablet

The data submitted are insufficient to support the approval of the 500 mg tablet, as only the 250 mg strength was used in the Phase 2 and Phase 3 clinical studies.

1. To obtain approval of the 500 mg chewable tablet, you must provide adequate additional data, from a bio-study or provide support for a bio-waiver.

Bio-Study: To obtain approval of the 500 mg tablet using a bio-study, you need to show that the 500 mg chewable tablets are clinically bioequivalent to two 250 mg chewable tablets. Given the apparent insensitivity of the serum concentration as a measure of lanthanum absorption, an alternative method of assessing bioequivalence should be proposed.

Bio-Waiver: To obtain approval of a bio-waiver for the 500 mg strength the following requirements need to be satisfied:

a. Clinical safety/efficacy data covering the dosing range of the higher strength.
b. Data demonstrating linear elimination kinetics over the therapeutic range.
c. Data demonstrating that the formulations of 250 and 500 mg strengths are proportionally similar.
d. Comparative dissolution profile data for the whole tablets using the same dissolution procedures.

2. Your proposed expiration date of 24 months for the 500 mg tablet is not acceptable. You will need to provide additional stability data.

CHEMISTRY

1. Drug Substance

Recent inspections of [ ] have revealed the presence of a degradation product, [ ] in the drug substance. Please explain why this was not documented in the NDA. If this degradation product is a recurring event, a method for monitoring it should be developed. The method should be included in the release and stability specifications for both drug substance and drug product with appropriate limits.

2. Drug Product Manufacture

In your February 4, 2003 response to Mr. Devaughn Edwards of the Office of Compliance you have stated that you will use [ ] in order to achieve full potency of the drug product at the time of manufacture. This is in apparent conflict with your agreement in the NDA amendment of December 20, 2002 where you state that the amount of lanthanum in the tablet formulation would be targeted to [ ] of label claim and the difference should be clarified.

3. Drug Product Stability and Specifications
After the Division has approved your new dissolution method and new acceptance criteria you should revise the drug product release and stability specifications accordingly. In addition, you should demonstrate that the stability of the 250 mg tablets using the new dissolution specifications is comparable to the stability documented in the original submission. For the 500 mg tablets, because of limited stability data available, we recommend that you initiate stability studies using the new dissolution specifications and generate sufficient data to assign a meaningful expiration date.

We remind you that a full response is needed to the comments and requests identified in our letter dated January 16, 2003, as you have committed to providing in your letter dated January 28, 2003.

Given the extent of the additional information needed, final labeling can not be considered at this time. As the additional information requested becomes available, revision of the proposed labeling will be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Cardio-Renal Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Robert Temple
2/28/03 10:49:06 AM

250 mg supplied in bottles of 100	NDC 54092-247-01
500 mg supplied in bottles of 100	NDC 54092-249-01

Storage

Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)

[See USP controlled room temperature]

Protect from moisture

Rx only

Manufactured for Shire US Inc.

Wayne, PA 19087-2088, USA

1-800-828-2088

Revision Date: 10/2004

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