CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022581Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022581 **COMPLETE RESPONSE**

Fresenius Medical Care North America
Attention: Sarah Tuller, J.D., RAC
Director of Pharmaceuticals, Regulatory Affairs
920 Winter Street
Waltham, MA 02451-1547

Dear Ms. Tuller:

Please refer to your July 20, 2009 New Drug Application (NDA), received July 21, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Phoslyra (calcium acetate) 667mg/5mL Oral Solution.

We acknowledge receipt of your amendments dated October 9, December 8, 18, 2009, March 1, 10, and April 21, 2010.

We also acknowledge receipt of your amendments dated May 12, and 17, 2010, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. 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 include annotations with the supplement number for previously-approved labeling changes.

FACILITY INSPECTIONS

During the recent inspections of the (b) (4) and Lyne Laboratories manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

There is evidence that calcium acetate, like other phosphate binders, has the potential to interact with other medications that are likely to be co-administered with Phoslyra. The drug label for PhosLo (calcium acetate gel caps) indicates that calcium acetate may decrease the bioavailability of tetracyclines. We are also aware of at least one published study that suggests that calcium acetate administration decreases the oral bioavailability of ciprofloxacin by ~50%;[1] there may be other published studies as well.

In addition, because this product will be utilized in children, we have concerns about its safety profile in pediatric populations. Phoslyra has not been shown to be efficacious, safe, or tolerated in children.

Based on the above, FDA has determined that if NDA 022581 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of drug interactions or identify an unexpected risk of hypophosphatemia or hypercalcemia in pediatric patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 022581 is approved, you will be required to conduct the following:

> Comprehensive in vitro screening studies to determine potential drug interactions with Phoslyra. Examples of drugs/drug classes that should be tested: tetracyclines, fluoroquinolones, beta blockers, thiazide diuretics, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, statins, sulfonylureas, glitazones, thyroid hormones, vitamin D/vitamin D analogue, warfarin, iron, and digoxin.
>
> Should any of these in vitro studies indicate variation in adsorption of ≥ 30%, in vivo evaluation may also be required.

[1] Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM. Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. Am J Kidney Dis. 2003 Dec; 42(6):1253-9.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected risk of hypophosphatemia or hypercalcemia in pediatric patients.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 022581 is approved, you will be required to conduct the following:

> A placebo-controlled dose response trial in a hyperphosphatemic pediatric dialysis population, followed by an open-label titration and maintenance phase followed by a placebo-controlled randomized withdrawal trial.

Any additional specific details of these required postmarketing study and trial, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved. If you request a Pediatric Written Request for this requirement, we are prepared to grant it.

If you complete these studies or the trial prior to re-submitting your application, you may include the final reports and relevant datasets in your Complete Response submission to facilitate review of the information.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling Text

8 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22581	ORIG-1	FRESENIUS MEDICAL CARE NORTH AMERICA	PHOSLYRA(CALCIUM ACETATE)ORAL SOL 667MG/

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

/s/

NORMAN L STOCKBRIDGE
05/21/2010