DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022581

NDA APPROVAL

Fresenius Medical Care North America
Corporate Headquarters
Attention: Laura Howson, MS, MBA
Manager, Regulatory Affairs
920 Winter Street
Waltham, MA 02451-1457

Dear Ms. Howson:

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

We acknowledge receipt of your amendments dated May 12, 17, 19, July 16, August 2, October 15, 2010 and February 17 (2) and April 11, 15 and 18, 2011.

The October 15, 2010, submission constituted a complete response to our 21 May 2010, action letter.

This new drug application provides for the use of Phoslyra (calcium acetate) 667 mg/ 5mL oral solution to reduce serum phosphorus in patients with end stage renal disease (ESRD).

We have completed our review of this application. 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. 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

As agreed, submit final printed carton and container labels, identical to the carton and immediate container labels you submitted on April 11, 2011 with the revisions to which you agreed on April 18, 2011 (below), as soon as they are available, but no more than 30 days after they are printed.

A. General Comments All Container Labels and Carton Labeling
    1. The route of administration statement and the "Only use the provided dosing cup..." statement are not prominent. Relocate both of these statements to the area below the statement of strength and above the colored rectangular bar. Additionally, use a bold font for both statements.
    2. Relocate the net quantity statement to the bottom of the principal display panel.

B. Container Labels
    1. Trade
        1. The product code statement is too prominent and is distracting in its current location. Relocate it to the bottom of the side panel and unbold the font.
        2. The "Rx Only" statement is too prominent. Decrease the size of the "Rx Only" statement and unbold the font.
    2. Professional Sample
        1. See Comment B.1.2, above.
        2. Relocate the product code to the bottom of the side panel.

C. Carton Labeling (Individual Carton, Trade and Professional)
        1. See Comment B.1.2, above.
        2. Relocate the product code to the bottom of the back panel.

D. Pull-off Insert Labeling
    1. The product code statement is too prominent and is distracting in its current location. Relocate it to the bottom of the panel and unbold the font.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22581**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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 (calcium acetate). 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%.

We have determined that 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.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1755-1 Comprehensive *in-vitro* screening evaluation to determine potential drug interactions with Phoslyra (calcium acetate).

The timetable you submitted on April 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2012
Study Completion Date:	11/2012
Final Report Submission:	03/2013

Submit the protocol to your IND with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(O)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(O)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(O)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1755-2 A multi-phase clinical trial in a hyperphosphatemic pediatric dialysis population, with a placebo-controlled dose-response phase, followed by an open-label titration and maintenance phase, followed by a placebo-controlled randomized withdrawal phase.

The timetable you submitted on April 11, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	03/2012
Trial Completion Date:	09/2013
Final Report Submission:	03/2014

Submit the clinical protocol to your IND for this product. Submit the final report to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see 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.

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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}
Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

NORMAN L STOCKBRIDGE
04/18/2011