

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022581Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 18, 2011

To: Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products

Through: Irene Z. Chan, PharmD, BCPS, Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Phoslyra (Calcium Acetate Oral Solution)
667 mg per 5 mL

Application Type/Number: NDA 022581

Applicant: Fresenius Medical Care North America

OSE RCM #: 2011-1215

1 INTRODUCTION

This review evaluates the revised labels and labeling received on April 12, 2011 for Phoslyra (Calcium Acetate Oral Solution) in response to a request from the Division of Cardiovascular and Renal Products.

1.1 REGULATORY HISTORY

This NDA was submitted on October 9, 2009. A Complete Response action was taken on May 21, 2010 due to manufacturing facilities deficiencies. The Applicant submitted a Class 2 Resubmission on October 18, 2010. The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the labels and labeling for Phoslyra in OSE Review 2009-2012, dated May 18, 2010. Our label and labeling comments were communicated to the Applicant on May 18, 2010.

1.2 PRODUCT INFORMATION

Phoslyra is a phosphate binder indicated for the reduction of serum phosphorus in patients with end stage renal disease. The recommended initial dose of Phoslyra for the adult dialysis patient is 10 mL with each meal. The dose should be increased gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Most patients require 15 mL to 20 mL with each meal. Phoslyra will be supplied in bottles containing 16 ounces. (b) (4)
(b) (4) Phoslyra will be supplied with a marked dose cup. Store Phoslyra at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

2 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate the labels and labeling of products. This review summarizes our evaluation of the container labels and carton labeling submitted by the Applicant in a paper submission received April 12, 2011 (see Appendices A through D).

- Trade: Container Label, Individual Carton Labeling, Shipper Carton Labeling
- Professional Sample: Container Label, Individual Carton Labeling, Shelf Carton Labeling, Shipper Carton Labeling
- Pull-Off Insert Labeling
- Insert Labeling (no image)

3 RESULTS AND DISCUSSION

The Applicant implemented the recommendations from our previous review, OSE Review 2009-2012. However, the layout and presentation of some information is not optimal. We also note the trade container label has a pull-off section; however, the Applicant did not submit the label that will remain attached to the bottle once the top portion is pulled off. Additionally, the Applicant did not submit a revised dosing cup, so it is unclear whether our previous recommendations for the dosing cup were implemented.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation identified areas where information on the labels and labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1 *Comments to the Division*. Section 4.2 *Comments to the Applicant* contains our

recommendations for the container labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Nina Ton, at 301-796-1648.

4.1 COMMENTS TO THE DIVISION

1. In the Dosage and Administration sections of Highlights of Prescribing and Full Prescribing Information the dosage range is stated “15 to 20 mL”. For clarity, we recommend the dosage unit (i.e., “mL”) be used in conjunction with the numerical designation in all instances where the dose is specified (i.e., revise to read “15 mL to 20 mL”).
2. In the Dosage and Administration section of Highlights of Prescribing, revise the statement “Titrate the dose every 2-3 weeks...” to read “Titrate the dose every 2 to 3 weeks”. Additionally, we note this statement is not in the Dosage and Administration section of Full Prescribing Information. Ensure the dosing and administration information is consistent between the Highlights of Prescribing and Full Prescribing Information sections of the insert labeling.
3. Remove the trailing zeros from Table 1 in Section 6.1 Clinical Trial Experience. The use of trailing zeros is on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations. As part of a national campaign to reduce medication errors related to error-prone medical abbreviations and dose designations, the FDA agreed not to approve labels and labeling that included the use of error prone abbreviations or dose designations.
4. In Section 17 Patient Counseling Information, healthcare providers are instructed to “advise patients who are taking oral medication where a reduction in bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour or three hours after Phoslyra”. However, it is not clear if the clinician should make the determination as to which medications should be separated from Phoslyra or if Phoslyra administration should be separated from other medications in general. We defer to the Clinical Pharmacology team regarding this determination.

4.2 COMMENTS TO THE APPLICANT

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.

5 Pages of Draft Labeling have been
Withheld in Full as b4 (CCI/TS)

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/s/

LORETTA HOLMES
04/18/2011

IRENE Z CHAN
04/18/2011

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
04/18/2011

PMR/PMC Development Template

This template should be completed by the PMR Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Comprehensive in vitro screening studies to determine potential drug interactions with Phoslyra.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2012</u>
	Study/Trial Completion:	<u>11/2012</u>
	Final Report Submission:	<u>03/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

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%. No dedicated drug-interactions studies have been conducted with calcium acetate so far. Hence there is an unmet need to understand the interaction potential of calcium acetate.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The proposed PMR will enable us to understand the interaction potential of calcium acetate with other concomitantly administered drugs and potential provide information to provide labeling instructions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The proposed PMR is an in vitro screening experiment that is aimed to evaluate the binding potential of calcium acetate with other drugs that are concomitantly administered in the indicated population.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

The proposed study will be an in vitro binding study exploring the binding potential of Phosra

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

The proposed PMR is an in vitro screening experiment that is aimed to evaluate the binding potential of calcium acetate with other drugs that are concomitantly administered in the indicated population.

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

RAJANIKANTH MADABUSHI
04/18/2011

PMR/PMC Development Template

This template should be completed by the PMR Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2012</u>
	Study/Trial Completion:	<u>09/2013</u>
	Final Report Submission:	<u>03/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Since the product formulation is a liquid, a study of the efficacy and safety of calcium acetate in a pediatric population is desirable.

Discussions about whether this study should be a post-marketing requirement or commitment have centered around the primary reason for the study: to investigate Phoslyra efficacy in pediatric patients. Studies demonstrating efficacy are typically postmarketing commitments, not requirements (whose primary endpoint is a safety issue). To compel the company to conduct an efficacy study under PREA is impossible in this case since Phoslyra is an orphan product. A memo by George Greeley (NDA 22581, 6/2/2010) explores the possibility of a requiring a postmarketing safety study (PMR) in this case. Although one could make a case that since this product is available in liquid form, the likelihood of pediatric use is high; at this time, neither efficacy nor safety in pediatric patients has been demonstrated, making it difficult to justify the PMR. Therefore, the described study will be listed as a post-marketing commitment in the action letter. However, if post marketing evidence (case reports, etc.) indicate a safety issue among pediatric patients, a post-marketing requirement may be considered to better clarify Phoslyra's place in therapy for hyperphosphatemia in pediatric patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the trial is to demonstrate efficacy of Phoslo in pediatric patients and therefore appropriate for a PMC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A pharmacodynamic study to explore the efficacy and safety of Phoslyra in pediatric patients with hyperphosphatemia using serum phosphate as a primary endpoint,

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MARY R SOUTHWORTH
04/18/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9858

M E M O R A N D U M

Date: May 18, 2010

From: George Greeley, Regulatory Health Project Manager
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products
Office of New Drugs

Re: Clarify whether the Division can require pediatric studies under a PMR
for a product receiving Orphan Designation.

Background

Sponsor: Fresenius Medical Care North America
Product: Phoslyra (calcium acetate)
Dosage Form: oral solution 667mg/5 ML
Route of Administration: oral
Indication (approved): (Rx) provided for the control of hyperphosphatemia in patients with
end stage renal disease

Application: NDA 22-581
Document Date: May 20, 2010

PMHS Response to Division Question

Division Clarify whether the Division can require pediatric studies under a PMR for a product receiving Orphan Designation.?

PMHS response: Section 505(o)(3) of the FDCA authorizes FDA to "...require a responsible person for a drug to conduct a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate..."

The Division can issue a PMR to require pediatric studies for products receiving Orphan Designation. Given that the Division has concerns about the safety profile in pediatric patients and that this product will be utilized in children, and that Phoslyra has not been shown to be efficacious, safe or tolerated in children, we recommend a PMR.

Please note that this PMR would be required under Section 505(o)(3), not under Section 505B (PREA).

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/s/

GEORGE E GREELEY
06/01/2010

LISA L MATHIS
06/02/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 18, 2010

To: Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products (DCRP)

Through: Kristina A. Toliver, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Phoslyra (Calcium Acetate Oral Solution)
667 mg/5 mL

Application Type/Number: NDA 022581

Applicant: Fresenius Medical Care North America

OSE RCM #: 2009-2012

1 INTRODUCTION

This review is written in response to a request from the Division of Cardiovascular and Renal Products for assessment of the container labels, carton and insert labeling for Phoslyra (Calcium Acetate Oral Solution), NDA 022581.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton, and insert labeling submitted as part of the October 9, 2009 paper submission (see Appendices A and B). Additionally, we evaluated the actual dosing cup submitted by the Applicant on February 19, 2010 (see Appendix C).

- Container Labels (b) (4) (b) (4)
- Carton Labeling (b) (4) (b) (4)
 - (b) (4)
 - (b) (4)
 - Shipper Carton
- Actual dosing cup
- Insert Labeling

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division*. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Nina Ton, at 301-796-1648.

3.1 COMMENTS TO THE DIVISION

1. In Highlights *Dosage and Administration* and Section 2 *Dosage and Administration* sections of the insert labeling there is the statement “Most patients require 15-20 mL...” We recommend the statement be revised to read: “Most patients require 15 mL to 20 mL...” in order to minimize any potential confusion that may occur with misinterpreting or overlooking the dash mark.
2. In Section 15 *How Supplied/Storage and Handling*, the Applicant lists (b) (4)

6 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/

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/s/

LORETTA HOLMES
05/18/2010

KRISTINA C ARNWINE
05/20/2010

DENISE P TOYER
05/20/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST
05/20/2010

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-581
APPLICANT	Fresenius Biotech North America, Incorporated
DRUG NAME	PHOSLYRA (calcium acetate oral solution)
SUBMISSION DATE	July 21, 2009
SEALD REVIEW DATE	April 30, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

9 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 BIOTECH NORTH AMERICA INC	PHOSLYRA(CALCIUM ACETATE)ORAL SOL 667MG/

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/s/

DEBRA C BEITZELL
04/30/2010
SEALD comments sent to DCRP on 4/30/10

LAURIE B BURKE
05/03/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: April 30, 2010

To: Lori Wachter – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Mark Askine – Associate Director
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 022581 PHOSLYRA (calcium acetate oral solution)

DDMAC has reviewed the proposed product labeling (PI) and container labeling for PHOSLYRA (calcium acetate oral solution) (Phoslyra), submitted for consult on April 19, 2010.

The following comments are provided using the updated proposed PI sent via email on April 19, 2010 by Lori Wachter. If you have any questions about DDMAC's comments, please do not hesitate to contact me.

Carton and Container Label

DDMAC has no comments on the carton and container labels at this time.

9 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
BIOTECH NORTH
AMERICA INC

PHOSLYRA(CALCIUM
ACETATE)ORAL SOL 667MG/

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/s/

EMILY K BAKER
04/30/2010



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team Review

Date: April 19, 2010 **Date Consulted:** May 1, 2010

From: Richardae Araojo, PharmD
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: The Division of Cardiovascular and Renal Products (DCRP)

Drug: Phoslyra (calcium acetate) oral solution; NDA 22-581

Subject: Pregnancy and Nursing mothers labeling for Phoslyra

Materials Reviewed: Phoslyra labeling

Consult Question: No animal studies have been performed with Phoslyra. Please provide language for the Pregnancy, Labor and Delivery, and Nursing Mothers sections of Phoslyra labeling.

BACKGROUND

On July 21, 2009, Fresenius Medical Care North America submitted a new drug application (NDA) for Phoslyra (calcium acetate). This NDA provides for a new oral solution formulation of calcium acetate. Phoslyra is a phosphate binder and is indicated for the control of hyperphosphatemia in patients with end stage renal disease. Calcium acetate, when taken with meals, combines with dietary phosphate to form an insoluble calcium-phosphate complex which is excreted in feces.¹ In studies, orally administered calcium acetate was systemically absorbed up to approximately 40% under fasting conditions and 30% under non-fasting conditions.¹ No animal studies have been conducted with Phoslyra. The Division of Cardiovascular and Renal Products (DCRP) consulted the Maternal Health Team to recommend language for the Pregnancy, Labor and Delivery, and Nursing Mothers subsections of Phoslyra labeling. This review will recommend language for the above mentioned sections of Phoslyra labeling.

SPONSORS PROPOSED LABELING

(Labeling includes division's edits. Labeling only presented for the Pregnancy, Labor and Delivery, and Nursing Mothers subsections of Phoslyra labeling.)

8. Use in Specific Populations

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women.

Animal reproduction studies have not been conducted with PHOSLYRA.

(b) (4)

(b) (4)

(b) (4)

8.2 Labor and Delivery

The effects of PHOSLYRA on labor and delivery are unknown.

8.3 Nursing Mothers

(b) (4)

DISCUSSION AND CONCLUSIONS

From a therapeutic perspective, Phoslyra is a phosphate binder; however, it can also be an oral source of absorbable calcium. When taken with meals, Phoslyra combines with dietary phosphate to form an insoluble calcium-phosphate complex which is excreted in the feces. Administration of Phoslyra during pregnancy or lactation is not expected to cause harm to a fetus

¹ Sponsor's proposed package insert for Phoslyra (calcium acetate) oral solution.

or nursing infant. However, because patients with end stage renal disease may develop hypercalcemia, appropriate and frequent monitoring of serum calcium levels is needed for maternal and fetal well being. Symptoms of maternal hypercalcemia may include headache, agitation, confusion, nausea, vomiting and abdominal pain, renal stones, polyuria, hypertension, pre-eclampsia, pancreatitis, and seizures.² Hypercalcemia in the fetus may cause intrauterine growth restriction, preterm delivery, intrauterine fetal demise, and perinatal death.² In addition, hypercalcemia during pregnancy has been associated with neonatal hypoparathyroidism and hypocalcemia with or without tetany.^{3,4}

The Maternal Health Team (MHT) and DCRP have worked collaboratively to develop pregnancy and nursing mothers labeling language that more clearly conveys available data and relevant concerns about the use of dialysis replacement solutions in a clinically meaningful way for prescribers. This same approach was used in developing language for Phoslyra. As with other dialysis treatments used to maintain normal electrolyte balance, the required standard statements for pregnancy and lactation labeling defined by 21 CFR 201.57 are not consistent with what is known about this product. Therefore, the recommended Phoslyra labeling language provided below does not include all of this standard language.

RECOMMENDATIONS

The MHT recommends the following language for the Pregnancy, Labor and Delivery, and Nursing Mothers subsections of Phoslyra labeling.

8.1 Pregnancy

Pregnancy Category C

Phoslyra contains calcium acetate. Animal reproduction studies have not been conducted with Phoslyra, and there are no adequate and well controlled studies of Phoslyra use in pregnant women. Patients with end stage renal disease may develop hypercalcemia with calcium acetate treatment [see *WARNINGS AND PRECAUTIONS (5.1)*]. Maintenance of normal serum calcium levels is important for maternal and fetal well being. Hypercalcemia during pregnancy may increase the risk for maternal and neonatal complications such as stillbirth, preterm delivery, and neonatal hypocalcemia and hypoparathyroidism. Phoslyra treatment, as recommended, is not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

8.2 Labor and Delivery

The effects of PHOSLYRA on labor and delivery are unknown.

8.3 Nursing Mothers

² Culbert EC, Schfirin BS. Malignant hypercalcemia in pregnancy: effect of pamidronate on uterine contractions. *Obstet Gynecol.* 2006;108(3 Pt 2);789-91.

³ Shani H, Sivan E, Cassif E, et al. Maternal hypercalcemia as a possible cause of unexplained fetal polyhydramnion: a case series. *Am J Obstet Gynecol.* 2008;199:410.e1-410.e5.

⁴ Sato K. Hypercalcemia during pregnancy, puerperium, and lactation: review and a case report of hypercalcemic crisis after delivery due to excessive production of PTH-related protein (PTHrP) without malignancy (humoral hypercalcemia of pregnancy). *Endocrine Journal.* 2008;55(6); 959-966.

Phoslyra contains calcium acetate and is excreted in human milk. Human milk feeding by a mother receiving Phoslyra is not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.

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/s/

RICHARDAE T ARAOJO
04/22/2010

Karen B FEIBUS
04/22/2010

I agree with the content and recommendations contained in this review.

LISA L MATHIS
04/27/2010

MEMORANDUM

TO: Lori Watcher
FDA/CDER/OND/ODEI/DCRP

FROM: Courtney C. Harper
FDA/CDRH/OIVD/DCTD

RE: NDA 22581
Fresenius Medical Care NA
Phoslyra

DATE: February 25, 2010

CDER/OND/ODEI/DCRP has requested a consult on NDA 22581 for Phoslyra, a drug indicated to lower serum phosphate in end stage renal disease patients on hemodialysis. The CDER review division has requested comment on whether the use of maltitol in the drug formulation would falsely register as "glucose" on a glucose meter and cause false high blood glucose test results.

Background

The presence of non-glucose sugars, found in certain drug and biologic formulations, has caused falsely elevated results in blood glucose monitors utilizing glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) methodology. This conclusion is supported by information in the scientific literature demonstrating that the presence of non-glucose sugars in the blood can lead to clinically meaningful increases in the glucose results measured using glucose dehydrogenase pyrroloquinoline-quinone (GDH-PQQ). When these falsely elevated blood glucose levels are used to guide insulin therapy, inappropriate dosing and administration has occurred and resulted in hypoglycemia, coma, and death. Manufacturers of GDH-PQQ meters have attempted to mitigate the risk by including labeling in the package inserts of these meters warning against this improper use, and have also implemented educational efforts on the correct use of the meters. Drug and biologic labeling has also been similarly modified. However, recent reports of deaths associated with incorrect use of these technologies calls into question whether labeling is sufficiently mitigating the risk posed by maltose interference. This led FDA to publish a Public Health Notification (and accompanying Advice for Patients) entitled "Potentially Fatal Errors with GDH-PQQ Glucose Monitoring Technology" in August 2009.

CDRH/OIVD/DCTD members were invited to attend a meeting of the Phoslyra drug review group on February 19, 2010. This new drug contains the disaccharide maltitol, and if administered, would expose patients to 9-12 g/day. The group discussed whether this sugar would be likely to cause false interference with glucose meters similar to the phenomenon described in the Public Health Notification.

Per the group discussion, maltitol is not absorbed at a high rate through the gut and is also unlikely to register on glucose meters as glucose due to its molecular structure. When metabolized, maltitol is converted into glucose and sorbitol. (See review consult from CDRH/OSEL for additional information). For these reasons, drugs containing maltitol are unlikely to cause false high blood glucose test results.

Conclusion

- Maltitol is unlikely, due to its molecular structure, to register on any glucose test strips as glucose.
- Maltitol is poorly absorbed into the blood and thus would not be present at high concentrations in blood samples.
- When metabolized, maltitol is converted into glucose and sorbitol. Sorbitol would not interfere with glucose test results. Glucose, when present in the blood, would be appropriately measured by blood glucose meters regardless of the source.
- For these reasons, the maltitol in Phoslyra is not likely to cause dangerous interference with blood glucose meter technologies.

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

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/s/

Lori A WACHTER

04/09/2010

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Protecting and Promoting Public Health
**FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
OFFICE OF DEVICE EVALUATION**

Consultative Memorandum

DATE: February 19, 2010

Requested by: Wachter, Lori, CDER, Division of Cardiovascular and Renal Products

Reviewed by: Irada S. Isayeva, Ph.D., Polymer Scientist, CDRH/OSEL/Division of Chemistry and Materials Science (DCMS)

Concurred by: Dinesh Patwardhan, Ph.D., DCMS, Director (Acting)

Subject: Maltitol Interference with Glucometers

Background

CDER received NDA 22-581 for Phoslyra (calcium acetate liquid), indicated for reduction of phosphate in end stage renal disease patients on hemodialysis. This product uses maltitol (b) (4)

This consult is written in response to CDER's question of "whether maltitol is absorbed and if it is, will it register as "glucose" on glucometers"?

Consult:

Maltitol (1,4 glucosylsorbitol) is a sugar alcohol (polyol) produced by hydrogenation of maltose obtained from starch (Figure 1). Maltitol is used as a sugar substitute with sweetness approaching that of sucrose.

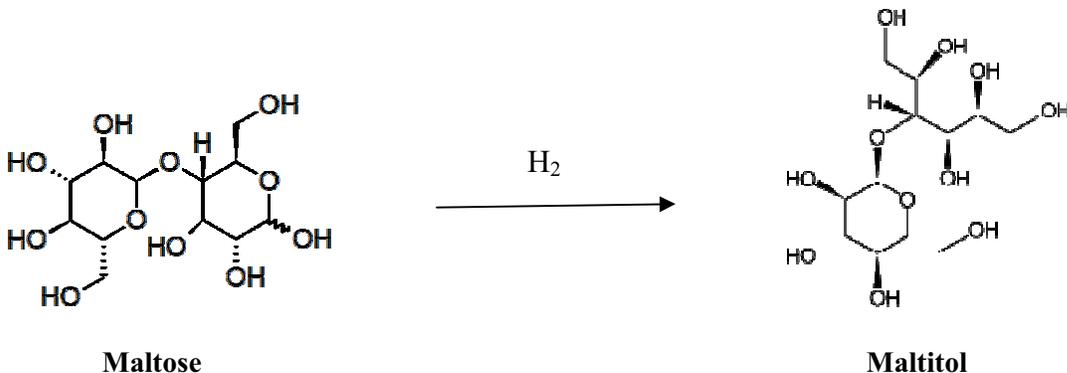


Figure 1

Maltose is disaccharide with reducing chain end, which shown to interfere with glucometers, specifically glucose dehydrogenase pyrroloquinoline quinine-based (GHD-PQQ). Contrary to maltose, maltitol is a non reducing sugar. During hydrogenation the reducing carbonyl group of maltose has been converted to primary stable alcohols, which will not readily participate in redox reactions that are technological basis for the glucometers. I have reviewed a large volume of scientific literature and did not find any reports that maltitol may interfere with enzyme-based glucose meters, neither glucose oxidase nor glucose dehydrogenase based.

In addition to the concern whether maltitol can directly interfere with glucometer readings, there may be a concern whether glucose produced as result of maltitol absorption and metabolism may cause a substantial increase in blood glucose concentration or not.

Maltitol is slowly hydrolyzed to glucose and sorbitol in small intestine by intestinal maltase (Figure 2) and further in the colon by the bacteria. It causes a small increase in blood glucose as compare to sucrose or glucose. The Glycaemic Index (GI) of maltitol is reported to be significantly lower that that of glucose (29-40 vs. 100).

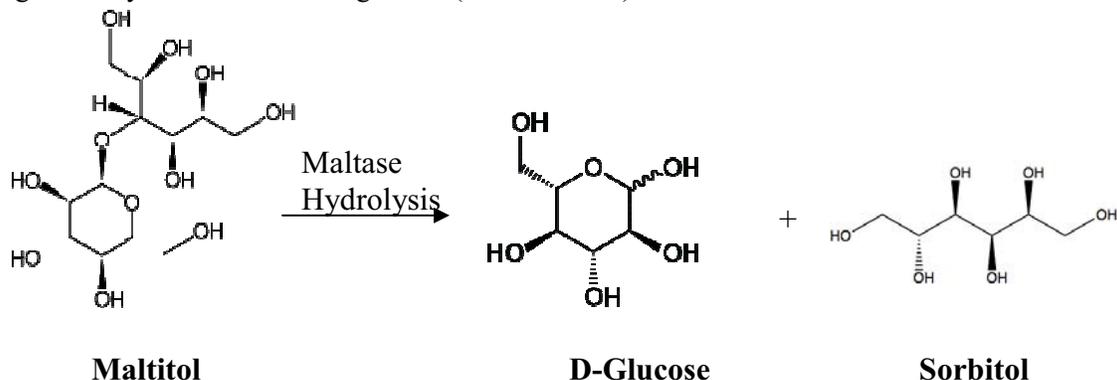


Figure 2

Based on the article by M.W. Kearsley and R.C. Deis (in Sweeteners and Sugar Additives in Food Ttechnology), the uptake of 25g of maltitol will cause the incremental raise in glucose, reaching its maximum of ~0.75mmol/L or 13.5mg/dL in 30minutes. An increase of blood glucose by 13.5 mg/dL is within ± 20 mg/dL error allowed for most glucometers. Given that the amount of maltitol (18g) in the maximum proposed daily dose of 90mL of PhosLo is less than 25g, the glucose raise due to maltitol from the proposed drug will be even smaller.

Sorbitol is also a sugar alcohol and it also metabolizes slowly. Studies in rats showed that sorbitol formed by intestinal hydrolysis of maltitol is appreciably excreted in urine. Sorbitol is also a product of glucose reduction, and should not be interfering with glucometers.

Conclusion:

- Given the specificity and reactivity of enzymatic glucose-based glucometers to glucose and in some cases, to other reducing sugars, the interference of non-reducing sugar alcohols such as maltitol with glucometers is less likely, provided that maltitol is of high purity (i.e., does not contain significant % of reducing sugars).
- Given the low Glycaemic Index of maltitol the raise in blood glucose will be small and may not be detected on glucometers.

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

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/s/

Lori A WACHTER

04/09/2010

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