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RESEARCH**

APPLICATION NUMBER:

022581Orig1s000

MEDICAL REVIEW(S)



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-581 Calcium acetate oral solution (Phoslyra) for reduction of serum phosphate.

Sponsor: Fresenius

Review date: 19 May 2010

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-581
HFD-110/Wachter

This memo conveys the Division's decision to issue a Complete Response letter for Phoslyra for reduction of serum phosphate in patients with end-stage renal disease.

This application has been the subject of reviews of CMC (Pinto; 31 March 2010), pharmacology/toxicology (Harlow; 12 and 15 March 2010), biometrics (Shuirmann; 8 April 2010), clinical (Moreschi; 2 February 2010). There is a comprehensive CDTL memo (Madabushi, 29 April 2010) with which I am in agreement.

The sponsor has two previous formulations of calcium acetate: tablets (NDA 19976) and gelcaps (NDA 21-160). Each tablet or gelcap contains 667 mg of calcium acetate. The current liquid formulation contains 667 mg of calcium acetate per 5 mL.

Per Division recommendations, the sponsor conducted a single, 3-period crossover study comparing excursions in serum and urinary calcium and phosphate following 3 days of treatment with the liquid formulation 6 x 5 mL, 6 gelcaps, and a similar calcium load in the form of calcium citrate.

Similar transient increases in serum calcium, urinary calcium, and urinary excretion of phosphate were observed. In comparisons of Phoslyra and the gelcaps, the similarities met usual criteria for bioequivalence.

The review team had some concerns over the maltitol in Phoslyra. This substance is considered GRAS and daily intake is not out of line with exposure from other approved products. There is some concern that maltitol can lead to diarrhea; maybe there was a hint of that in the crossover study. Labeling reflects the possibility, particularly if Phoslyra is used with other maltitol-containing products. CDRH was consulted and did not regard maltitol to be a risk for affecting glucometers.

The only issue barring approval is failure of a facility site inspection, not resolvable before we take an action.

There are two post-marketing requirements.

The sponsor does not have good drug-drug interaction studies with any formulation of calcium acetate. The sponsor will be asked to conduct a battery of in vitro tests, to be followed, as indicated, with in vivo studies.

Phoslyra is likely to be used in children with end stage renal disease. Because the product is orphan, PREA does not apply. Nevertheless, there is a safety issue with its use that needs to be resolved. We can offer them a Written Request for the necessary safety study. This has been cleared through SRT.

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/

NORMAN L STOCKBRIDGE
05/19/2010

CLINICAL SAFETY REVIEW

Application Type 22-581
Application Number(s) 1
Priority or Standard Standard

Submit Date(s) July 20, 2009
Received Date(s) July 21, 2009
PDUFA Goal Date May 21, 2010
Division / Office DCaRP

Reviewer Name(s) Gail Moreschi, MD,MPH,FACP
Review Completion Date January 15, 2010

Established Name Calcium acetate
(Proposed) Trade Name Phoslyra™
Therapeutic Class Phosphate binder
Applicant Fresenius

Formulation(s) Liquid
Dosing Regimen tid with meals
Indication(s) Hyperphosphatemia
Intended Population(s) End Stage Renal Disease

1 Recommendations/Risk Benefit Assessment

From a clinical viewpoint this study has demonstrated that liquid PhosLo is tolerated for a short term in normal volunteers. This study has not determined whether or not patients with chronic renal disease will tolerate this new formula. However, since the liquid formula is similar to the approved formula, this reviewer recommends approval.

Also, this clinical reviewer recommends that a review by the Office of Clinical Pharmacology be conducted to evaluate in greater depth the study design, execution, and results vis-a-vis bioequivalence reported by the Sponsor to support approval of this new formulation. Additionally, it needs to be determined whether or not maltitol in the liquid calcium acetate solution will influence the monitoring of blood glucose levels.

Recommendations for Postmarket Requirements

(b) (4) or PhosLo ultimately may be used in the pediatric population. Therefore, a Written Request must be encouraged although PhosLo received an Orphan Drug approval letter dated December 22, 1988.

2 Introduction and Background

This new drug application is for Phoslyra™, Calcium Acetate Oral Solution 667mg/5mL. This is a new dosage form of the already approved calcium acetate as solid formulations: PhosLo® Tablets, NDA 19-976, approved in 1990 and PhosLo® Gelcaps, NDA 21-160, approved in 2001. The decision for this new formula was market-driven and was not related to safety or efficacy. The NDA 19-976 for PhosLo® Tablets remains active and PhosLo® has more than 15 years of post-marketing experience.

The calcium acetate oral solution formulation was designed to be bioequivalent with the already approved PhosLo® Tablets and Gelcaps. The oral solution is to have the identical calcium acetate dosage contained in one tablet or gelcap dissolved into 5mL of an oral solution.

Under an agreement with the Division of Cardiovascular and Renal Products there was only one clinical study completed in support of this new drug application. The Study: “Randomized, Controlled, 3-arm, Open Label, Cross-over Bioequivalence Study Comparing Liquid PhosLo vs. PhosLo Gelcaps using Calcium Citrate as a Positive Control in Healthy Volunteers” was performed under IND (b) (4) for calcium acetate and this study is LP-RTG-01-01.

3 Study Protocol

This study was designed as a randomized, controlled, 3-arm, open label, cross-over Phase I study evaluating the bioequivalence of the investigational drug, liquid PhosLo compared to PhosLo Gelcaps. Calcium citrate provided a positive control profile for both the serum and urine 24 hr profiles. Approximately 40 subjects were planned to be enrolled.

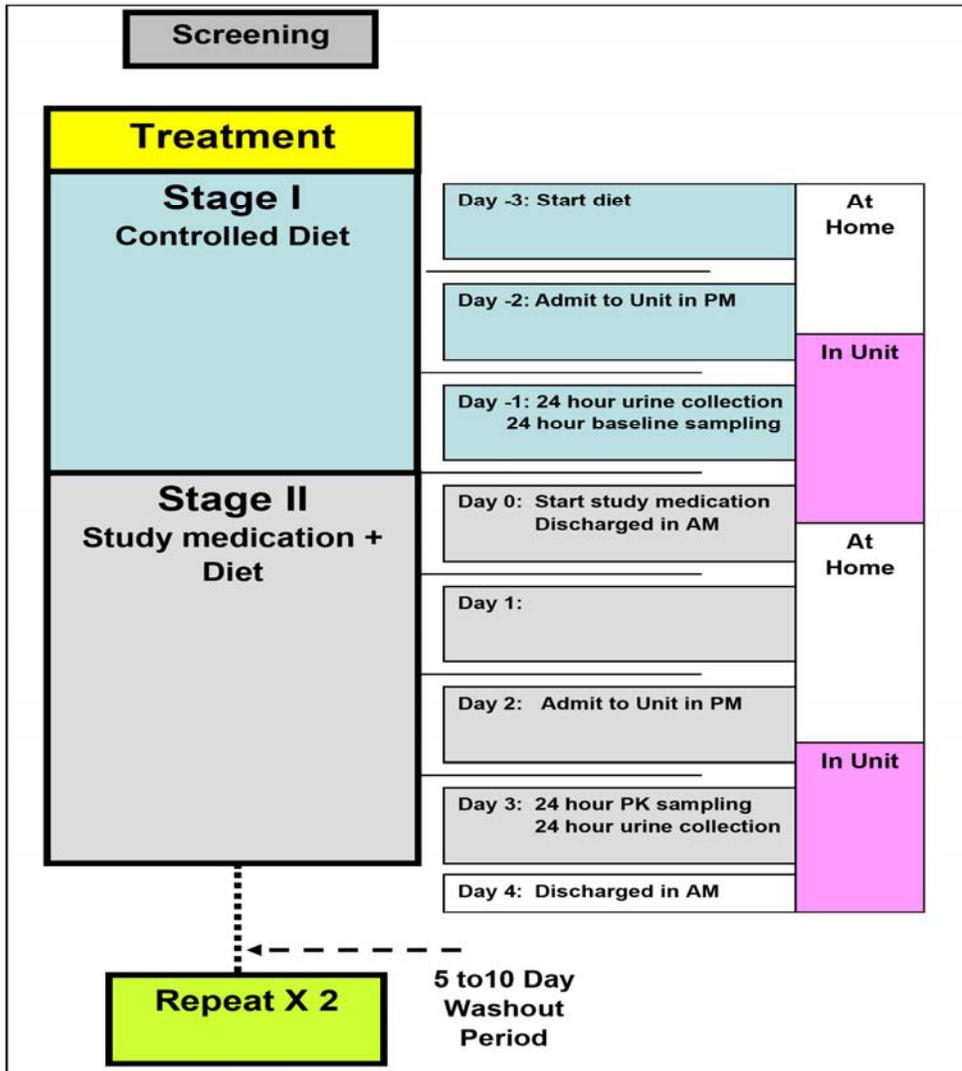
OBJECTIVES:

Primary Objective: To demonstrate the bioequivalence of liquid PhosLo to PhosLo Gelcaps with respect to urinary calcium excretion and serum phosphorus levels in healthy subjects.

Secondary Objectives: To compare change in urinary phosphorus and serum calcium before and after dosing with liquid PhosLo vs. PhosLo Gelcaps in healthy subjects. To compare liquid PhosLo to PhosLo Gelcaps with respect to serum glucose and insulin levels in healthy subjects.

Subjects who completed the tolerance test to oral liquid PhosLo were randomized (1:1:1) to 1 of 3 treatment sequences. The study included 4 periods; a Screening period (up to 25 days) and 3 sequential study treatment periods. The sequential order of the 3 treatment periods (liquid PhosLo, PhosLo Gelcaps, and calcium citrate) was determined by randomization. Approximately the same amount of elemental calcium, 1000 mg, was administered in each dose for each treatment arm. Each treatment period was separated by a 5 to 10 day washout period. Each treatment period was divided into 2 stages. At Stage I, subjects were started on the controlled study diet. At Stage II, subjects were started on study medication and continued on the controlled study diet. This is shown in the following figure.

Figure 1 - Study Design



Subjects of both sexes and of any ethnic origin were enrolled in this study if they met the Inclusion and Exclusion criteria for normal volunteers. These criteria are acceptable.

Each subject received oral liquid PhosLo, oral PhosLo Gelcaps, and the oral calcium citrate positive control, taken t.i.d. with meals. The dosage of liquid PhosLo was 30 mL t.i.d. with a concentration of 667 mg calcium acetate per 5 mL. A daily dose of 90 mL of liquid PhosLo is equivalent to 18 PhosLo Gelcaps, which is the maximum expected daily dose in ESRD patients. The PhosLo Gelcap starting dose according to the Prescribing Information is 2 gelcaps per meal, with an expected dose of 3–4 gelcaps per meal, for a total expected daily

dose of 12 gelcaps. The dosage level was also determined in consideration of the study population, healthy adults.

This study was designed to compare the PK of liquid PhosLo and PhosLo Gelcaps to determine bioequivalence. The measurements utilized represent standard assessments to determine urinary calcium excretion and serum phosphorus. This study was open label and no blinding was utilized.

STUDY VISITS:

Evaluations included physical examination, vital signs, baseline serum measurement, 24 hr urine collection, 24 hr PK sampling, ECG and 6 hr serum glucose and insulin profile. PK levels were measured on pre-established study visits within each treatment period:

- Screening Period: Day -30 to Day -5
- Treatment Period Stage I: Day -3 to Day 0
- Treatment Period Stage II: Day 0 to Day 3
- Washout Period: 5-10 days

At the conclusion of the washout period, subjects began the next treatment period. There were 3 treatment periods in this study

The schedule of assessments is shown in the following table.

Table 1 - Schedule of Assessments

	Screening	Randomization	Controlled Diet ⁷ Stage I			Controlled Diet + Study Medication ⁷ Stage II				Washout ¹¹	EOS Or Early Withdrawal	
			-3	-2	-1	0	1	2	3			4
Time (days) relative to start of study medication administration	-30 to -5	-4	-3	-2	-1	0	1	2	3	4	5-10	
Informed consent	X											
Screening labs and drugs of abuse ¹	X											
Pregnancy test (urine) ²	X				X							
Inclusion and exclusion criteria	X											
Demography, medical history	X											
Physical examination	X											
Overnight at Phase I unit				X ⁸	X			X ⁸	X			
Discharged from Phase I unit						X				X		
Controlled diet			X	X	X	X	X	X	X			
24 hr baseline serum sampling ³					X							
Assignment of study medication kit		X										
Administration of study medication	X ⁶					X	X	X	X ¹⁰			
24 hr urine collection ⁴					X				X			
24 hr PK serum sampling ⁵									X			
Vital signs (temperature, BP, pulse rate, RR)	X			X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹		
ECG	X											
Adverse events	X			X	X	X		X	X	X		
Concomitant medications	X			X	X	X		X	X	X		
Follow-up telephone call												X

BP=Blood Pressure; ECG=Electrocardiogram; PK=Pharmacokinetic; RR=Respiratory Rate

1. Screening labs included: a serum chemistry panel with Liver function tests (LFT), calcium, phosphorus, insulin, glucose, albumin, sodium, potassium and creatinine; a complete blood count (CBC), 25-vitamin D, 1, 25-dihydroxy vitamin D, iPTH, a coagulation panel, serology for HIV, Hepatitis B and Hepatitis C; and routine urinalysis.
2. Pregnancy test was only performed if subject was of childbearing potential. The pregnancy test must not have been older than 72 hr prior to administration of the first study medication dose.
3. Baseline serum calcium and phosphorus samples were collected at 0.00 (prior to meal and at fasting state), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 18.00, 24.00 hr relative to morning meal. Baseline serum glucose samples were collected at 0.00 (prior to meal and at fasting state), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00 and 6.00 hr relative to morning meal. Baseline serum insulin samples were collected at 0.00 (prior to meal and at fasting state), 1.00, 2.00, 3.00, 4.00, 5.00 and 6.00 hr relative to morning meal.

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4. 24 hr urine sample were collected in fractions every 2 hr, up to 8 hr, then from 8-12 hr, and then from 12-24 hr. If subjects could not void every 2 hr, urine was collected as close to the defined time intervals as possible
5. PK serum calcium and phosphorus samples were collected at 0.00 (prior to meal and at fasting state), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 18.00, 24.00 hr relative to morning meal and final dose. PK serum glucose samples were collected at 0.00 (prior to meal and at fasting state), 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00 and 6.00 hr relative to morning meal and final dose. PK serum insulin samples were collected at 0.00 (prior to meal and at fasting state), 1.00, 2.00, 3.00, 4.00, 5.00 and 6.00 hr relative to morning meal and final dose.
6. A partial dose of 10 mL of liquid PhosLo was given to the subject during screening to assess tolerability. A minimum of 3 days washout period followed taste test dose prior to starting the controlled diet on Day -3.
7. Stages I and II were repeated for each of the 3 treatment periods.
8. Subjects were admitted to the Phase I unit prior to their evening meal.
9. Vital signs were measured prior to each meal on the days the subject was in the Phase I unit.
10. Study medication was administered during breakfast and then discontinued.
11. Washout period was repeated following treatment periods 1 and 2 only.

The statistical review will establish the statistical methods utilized and the bioequivalence of PhosLo liquid and PhosLo Gelcaps. Unless otherwise specified there was no substitution of missing data. Missing data were handled as 'missing' in the statistical evaluation.

4 Study Subjects

A total of 46 subjects were randomized to 1 of 3 sequence groups. A summary of subject disposition is presented in the following table.

Table 2 - Subject Disposition

	Sequence I	Sequence II	Sequence III	Total
Number of subjects randomized	15	15	16	46
Number that did not complete the study at any stage	3 (20.0%)	3 (20.0%)	4 (25.0%)	10 (21.7%)
Reason for Early Withdrawal				
Discontinuation requested by investigator - failed to disclose medical history	0	1 (6.7%)	0	1 (2.2%)
Discontinuation requested by investigator - syncopal episode	1 (6.7%)	0	0	1 (2.2%)
Other – Positive pregnancy test	0	1 (6.7%)	0	1 (2.2%)
Withdrew consent	2 (13.3%)	1 (6.7%)	4 (25.0%)	7 (15.2%)

Percentages were based on number of subjects randomized.

Sequence I, from Period 1 to 3: liquid PhosLo, PhosLo Gelcaps, calcium citrate.

Sequence II, from Period 1 to 3: PhosLo Gelcaps, calcium citrate, liquid PhosLo.

Sequence III, from Period 1 to 3: Calcium citrate, liquid PhosLo, PhosLo Gelcaps

A total of 10 subjects were withdrawn from the study: 7 (15.2%) subjects withdrew consent and 3 (6.5%) of subjects were withdrawn by request of the Investigator. Data from these subjects was not included in the PK analysis.

Protocol Deviations

The following table provides a summary of protocol deviations by category.

Table 3 - Protocol Deviations

Category	Number of Deviations
Adequate contraception	1
Diet	2
Dosing	5
Informed Consent Form (ICF)	7
Inclusion/Exclusion (I/E) criteria	6
Laboratory evaluations	27
Visits	2
Vital Signs	256

None of the deviations resulted in exclusion of subjects from an analysis or affected interpretation of the results.

Demographic Characteristics

Subjects were healthy adults. A summary of demographic parameters is shown in the following table.

Table 4 - Summary of Demographic Parameters

Demographic Parameters		Total N=46
Age (years)	n	46
	Mean (SD)	40.6 (14.7)
	Min-Max	19.0- 70.0
Gender	Male	18 (39.1%)
	Female	28 (60.9%)
Race	Black/African American	6 (13.0%)
	White	40 (87.0%)
Ethnicity	Not Hispanic or Latino	46 (100.0%)
Reproductive Status	Male or Female of Childbearing Potential with Contraception	36 (78.3%)
	Postmenopausal Female	5 (10.9%)
	Surgically Sterilized	5 (10.9%)
Weight (kg)	n	46
	Mean (SD)	72.6 (11.4)
Height (cm)	n	46
	Mean (SD)	170.5 (8.4)
BMI (kg/m ²)	n	46
	Mean (SD)	24.9 (2.7)

The majority of subjects were white and female. The majority of subjects were male or female of childbearing potential with a mean (SD) age of 40.6 years. None of the subjects were Hispanic. There were no significant medical histories findings; all subjects were healthy volunteers.

5 Safety Evaluation

Extent of Exposure

In this study, healthy volunteers received each of the following study medications t.i.d. with meals from Day 0 through Day 2 and 1 morning dose on Day 3 (Stage II) of the trial, in 3 sequential treatment periods (A, B or C):

- A. 30 mL liquid PhosLo (667 mg calcium acetate/5 mL; 169 mg elemental calcium/5 mL),
- B. 6 PhosLo Gelcaps (667 mg calcium acetate/gelcap; 169 mg elemental calcium/gelcap)
- C. 5 calcium citrate caplets as a positive control (950 mg calcium citrate/caplet; 200 mg elemental calcium/caplet)

A daily dose of 90 mL of liquid PhosLo is equivalent to 18 PhosLo Gelcaps, which is the maximum expected daily dose in end stage renal disease (ESRD) patients. The PhosLo Gelcap starting dose according to the Prescribing Information is 2 gelcaps per meal, with an expected dose of 3–4 gelcaps per meal, for a total expected daily dose of 12 gelcaps. The dosage level was also determined in consideration of the study population, which comprised healthy adults.

Collection of plasma and urine for the assessment of the pharmacodynamic, pharmacokinetic, and safety parameters was initiated immediately prior to the final dose of the study medication on Day 3 and continued for 24 hours post dosing. As the 24-hour post-treatment sample collection period included only one dose and several meals, comparability was also assessed over the first 6 hours following the final dose.

Adverse Events

There were no deaths or SAEs during this study. There were also no AEs leading to withdrawal. Essentially, no drug-related safety concern was raised from the safety data in this study.

The majority of AEs was mild in severity, transient, and resolved without sequelae. Six subjects experienced 11 moderate AEs; the majority (10/11) of which were considered not related to study treatment. One AE of transient elevated BP was considered possibly related to study treatment. The majority of AEs occurred in Stage II of the study when subjects were restricted to the study diet and received study medication. In Stage II, there was no overall difference observed in the types of AEs or their severity between the liquid PhosLo and the PhosLo Gelcap treatment groups; the majority of drug-related AEs were mild GI disorders. Two subjects who received liquid PhosLo experienced moderate AEs. One subject experienced moderate ongoing events of arthralgia and peripheral edema in the left knee which were considered not related to the study treatment. Another subject experienced moderate increased BP which resolved after 1 day and was considered possibly related to the study treatment.

Table 5 - Summary of Adverse Events (Stage II and Washout)

Stage	AEs (% subjects)	Treatment Group		
		Liquid PhosLo	PhosLo Gelcaps	Calcium Citrate
Stage II – Study medication and Controlled Diet	N	38	38	38
	Total Subjects with at least 1 AE	22 (57.9%)	17 (44.7%)	5 (13.2%)
	Mild	20 (52.6%)	17 (44.7%)	5 (13.2%)
	Moderate	2 (5.3%)	0	0
	Total Number of Episodes	33	23	5
Washout – No Study Diet and No Drug	N	37	37	38
	Total Subjects with at least 1 AE	2 (5.4%)	1 (2.7%)	3 (7.9%)
	Mild	1 (2.7%)	1 (2.7%)	3 (7.9%)
	Moderate	1 (2.7%)	0	0
	Total Number of Episodes	2	1	5

AE=adverse event

Percentages were based on total number of subjects in each stage and treatment (N).

A subject with multiple events in 1 Preferred Term (PT) was counted only once for that PT, using the event with the greatest severity. A subject with multiple events in 1 System Organ Class (SOC) was counted only once for that SOC, using the event with the greatest severity. Subjects with missing PK or AE dates could not have their data defined (Subject 1067-030, moderate tooth extraction).

The majority of the drug-related AEs in Stage II who received active study medication (liquid PhosLo or PhosLo Gelcaps) were mild GI disorders. Diarrhea occurred more frequently in the liquid PhosLo group compared to the PhosLo Gelcaps (5 subjects vs. 1 subject, respectively). The diarrhea was transient and resolved without sequelae. AEs reported by subjects who received the positive control (calcium citrate) were distinct from subjects who received active study medication and characterized by a lower total number of AEs with 1 GI-related AE in Stage II.

In Stage II, the most common drug-related AEs (occurring in ≥ 2 subjects) were mild GI disorders. For subjects who received liquid PhosLo, these AEs included nausea (9 subjects), diarrhea (5 subjects), abdominal pain (2 subjects) and gastroesophageal reflux disease (2 subjects). Subjects who received PhosLo Gelcaps experienced the following AEs: nausea (10 subjects) and vomiting (2 subjects). Subjects who received calcium citrate had mild AEs that included 2 subjects with nervous system disorders (headache) and 2 subjects with metabolism and nutrition disorders (anorexia).

Table 6 - Summary of Study-Related Adverse Events (Stage II and Washout)

Stage	MedDRA Preferred Term All Adverse Events (Drug-Related*)	Treatment Groups		
		Liquid PhosLo	PhosLo Gelcaps	Calcium Citrate
Stage II – Study medication and Controlled Diet	N	38	38	38
	Nausea	9 (9)	10 (10)	0
	Diarrhea	5 (5)	1 (1)	0
	Abdominal Pain	2 (2)	0	0
	Abdominal Pain Upper	1 (1)	0	0
	Abdominal Distention	1 (1)	0	0
	Flatulence	1 (1)	0	0
	Gastroesophageal Reflux Disease	2 (2)	0	0
	Stomach Discomfort	1 (1)	0	0
	Vomiting	0	2 (2)	0
	Dyspepsia	1 (1)	0	1 (1)
	Dysuria	1 (1)	0	0
	Feeling Hot	2 (2)	0	0
	Blood Pressure Increased	1 (1)	0	0
	Anorexia	2 (2)	1 (1)	2 (2)
	Headache	1 (1)	5 (3)	2 (2)
Dizziness	1 (1)	1 (1)	0	
Washout – No Study Diet and No Drug	N	37	37	38
	Nasal Congestion	0	1 (1)	0
	Abdominal Pain Upper	0	0	1 (1)
	Decreased Appetite	0	0	1 (1)

*Based on drug-related adverse events, which were marked by the Investigator as having an Unlikely, Possible, Probable or Certain Relationship to study medication.
 A subject with multiple events in 1 Preferred Term (PT) was counted only once for the PT.
 Subjects with missing PK or AE dates could not have their stage defined.

There were no SAEs, severe AEs or AEs leading to withdrawal based on abnormal laboratory values. Several subjects exhibited mild hypoglycemia (defined as serum glucose <65 mg/dL) at repeated time points. Of the 2033 serum glucose results (baseline and treatment), approximately 7.6% (155) fell in the hypoglycemic range of <65 mg/dL. More than half of those hypoglycemic values were ≥60 mg/dL, or within 5 mg/dL of the hypoglycemia definition. Only 1 value (62 mg/dL) occurred at a fasting (0 hr) time point. The hypoglycemic values were split almost evenly between baseline (53%) and treatment (47%) days.

The analysis of the 6-hour glucose and insulin levels in serum did not indicate any significant influence of the maltitol in the liquid formulation on serum glucose control. The glucose and insulin responses were comparable between treatment groups.

6 Discussion of Safety Findings

This Study LP-RTG-01-01 demonstrates safety of the new liquid formula in normal volunteers when utilized for short terms. Liquid PhosLo is tolerated except for mild GI symptoms which pass without treatment in normal persons. Diarrhea was more common in the liquid PhosLo treatment group and may be related to the maltitol in the formulation. However, to this clinical reviewer, this study does not demonstrate that patients with chronic renal disease will be able to tolerate the new liquid PhosLo. The gut permeability is different in patients with chronic renal disease. Also, many of these patients have diabetes with GI motility problems. Although approval is recommended, it is hard to determine at this point how well the new liquid formula will be tolerated in the chronic renal failure population.

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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GAIL I MORESCHI
02/02/2010