CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22-581
Supporting document/s:	
Applicant's letter date:	July 20, 2009
CDER stamp date:	July 21, 2009
Product:	Calcium acetate (Phoslyra™)
Indication:	Control of hyperphosphatemia
Applicant:	Fresenius Medical Care North America
Review Division:	Cardiovascular and Renal Products
Reviewer:	Patricia P. Harlow, Ph.D.
Supervisor/Team Leader:	Albert DeFelice, Ph.D.
Division Director:	Norman Stockbridge, MD, Ph.D.
Project Manager:	Lori Wachter

Template Version: December 7, 2009

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Some of the information in this document is considered proprietary and not for public disclosure.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

This document contains additional information obtained during the nonclinical review of NDA 22-581. Some of this information is considered proprietary and not for public disclosure.

1.1 Recommendations

1.1.1 Approvability

The use of maltitol is approvable as an excipient in the liquid formulation of PhosLo® calcium acetate oral solution, a new dosage form of calcium acetate, which is already approved as two solid formulations: PhosLo® Tablets (NDA 19-976 approved 1990) and PhosLo® Gelcaps (NDA 21-160 approved 2001).

1.1.2 Additional Non Clinical Recommendations

None.

1.1.3 Labeling

Polyol sweeteners, like maltitol, have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. Although the maximum recommended dosage of liquid PhosLo® (90 mL per day or 18 gm of maltitol) is less than the threshold level of maltitol (30 gm) reported to induce laxative effects, maltitol is used in many food products and nutritional supplements, such as Nepro® designed specifically for patients with chronic kidney failure on dialysis. Therefore, the labeling for liquid PhosLo® should indicate that liquid PhosLo® contains maltitol, which may induce laxative effects.

1.2 Brief Discussion of Nonclinical Findings

Maltitol, a disaccharide sugar alcohol, is composed of glucose and sorbitol. Maltitol and maltitol syrups are self-affirmed GRAS based on petition to the FDA. The European Union's Scientific Committee on Food (SCF) and the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) concluded that maltitol is safe and assigned the safest category of an acceptable daily intake (ADI) for maltitol of "not specified."

Literature database searches identified no studies describing the specific use of orally administered maltitol in patients with renal impairment, renal insufficiency, chronic kidney disease, or in patients with end-stage renal disease who require hemodialysis. However, maltitol is a component of Nepro®, a nutritional supplement designed for patients with chronic kidney disease on dialysis (Stage 5). (b) (4)

(b) (4)

Because the consumption of maltitol in PhosLo® is anticipated to be 9-12 gm per day, a higher event rate is likely. Also, given that maltitol is used in many food products and nutritional supplements, the labeling for liquid PhosLo® should indicate that liquid PhosLo® contains maltitol, which may induce laxative effects.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

62-54-4

2.1.2 Generic Name

Calcium acetate, USP, oral solution

2.1.3 Code Name

Phoslyra™

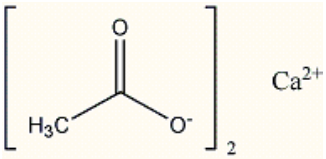
2.1.4 Chemical Name

Calcium acetate

2.1.5 Molecular Formula/Molecular Weight

Molecular Formula: $C_4H_6CaO_4$
Molecular Weight: 158.2

2.1.6 Structure



2.1.7 Pharmacologic class

Phoslyra™ calcium acetate oral solution is a phosphate binder.

2.2 Relevant IND/s, NDA/s, and DMF/s

Phoslyra™ calcium acetate oral solution is a new dosage form of calcium acetate a product already approved as two solid formulations: PhosLo® Tablets (NDA 19-976 approved 1990) and PhosLo® Gelcaps (NDA 21-160 approved 2001).

2.3 Clinical Formulation

2.3.1 Drug Formulation

The formulation for Phoslyra™ calcium acetate solution is summarized in Table 1 along with the daily intake of each of the solution components. Patients will take up to 30 mL of Phoslyra™ as a single dose three times per day. The maximum daily dose of Phoslyra™ results in the consumption of 12 grams of calcium acetate and 18 grams of maltitol.

Table 1: Reviewer's modification of Sponsor's Summary of the Phoslyra™ Formulation

Sponsor's table		Reviewer's addition	
Ingredient	Concentration per 5mL	Maximum amount per single dose	Maximum amount per day
Calcium Acetate USP	*667.0 mg/5mL	4002 mg/30 mL	(b) (4)
(b) (4) Maltitol NF	1000 mg/5mL	(b) (4)	
Glycerin USP	(b) (4)		
Propylene Glycol USP			
Magnasweet 110			
Sucralose NF			
Methylparaben NF			
Povidone K25 USP			
Artificial Black Cherry Flavor (b) (4)			
Menthol Flavor, Natura (b) (4)			
Purified Water USP			
*On anhydrous basis			

2.3.2 Comments on Novel Excipients

The reader is referred to the nonclinical review finalized in DARRTS on 03/12/10 for the evaluation of publically available information on the safety, absorption, excretion of one of the excipients, maltitol, in liquid PhosLo® (b) (4)

(b) (4)

Use of maltitol in the indicated population

The sponsor's and reviewer's literature database searches identified no studies describing the specific use of orally administered maltitol in patients with renal impairment, renal insufficiency, chronic kidney disease, or in patients with end-stage renal disease who require hemodialysis.

The nutritional supplement, Nepro® with Carb Steady® is designed specifically for patients with chronic kidney disease on dialysis (Stage 5) (b) (4)

(b) (4)

(b) (4) other diabetic food products and supplements contain maltitol. For example, one Glucerna® snack bar contains 10 gm maltitol per bar. The use of liquid PhosLo® in combination with other products containing maltitol is likely to increase the adverse event rate for gastrointestinal effects even further in the population of renal failure patients on dialysis.

(b) (4) cites eight publications of studies of hemodialysis patients in which Nepro® was used. However, all of these studies used previous formulations of Nepro that did not contain maltitol.

Use of Maltitol in Other Drug Products

The FDA "Inactive Ingredient list for Approved Products" (last updated January 13, 2010) indicates that maltitol is approved for oral administration in solution at a maximum potency of 65% (w/v). In contrast, PhosLo contains 20% maltitol (w/v).

One approved drug product that contains maltitol is entecavir (Baraclude; NDA 21798). The initial approved formulation contained (b) (4) of maltitol (b) (4) which typically contains (b) (4) (b) (4) If maltito (b) (4) contains a minimum of (b) (4) maltitol, then the minimum amount of maltitol in the approved product is 325 mg/mL. (b) (4) The maximum recommended daily dose of entecavir, (b) (4), now contains (b) (4) maltito (b) (4)

Another approved drug product, Keppra® (levetiracetam) contains (b) (4) maltitol (b) (4) per (b) (4) If maltitol (b) (4) contains a minimum of (b) (4) maltitol, then the minimum amount of maltitol in the approved product is (b) (4) The recommended adult daily dosage is (b) (4) r (b) (4) maltitol (b) (4) or (b) (4) maltitol (b) (4)

Although the concentration of maltitol in liquid PhosLo® is only 20% (w/v), the total average daily dose of maltitol for patients taking liquid PhosLo® (9-12 gm) is greater than the daily dosages of maltitol in levetiracetam or entecavir.

2.3.3 Comments on Impurities/Degradants of Concern

Not applicable.

2.4 Proposed Clinical Population and Dosing Regimen

Patients with end stage renal disease will take the liquid formulation of Phoslyra™ with meals three times a day.

2.5 Regulatory Background

Phoslyra™ calcium acetate oral solution (liquid PhosLo®) is a new dosage form of calcium acetate which is already approved as two solid formulations. PhosLo® Tablets were approved in 1990 under NDA 19-976 and PhosLo® Gelcaps were approved in 2001 under NDA 21-160.

3 Studies Submitted

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission. The sponsor referred to NDA 19-976 Volume 1.2 Section 314.50 d(2) Nonclinical Pharmacology and Toxicology for Module 4 Nonclinical Study Reports and, if necessary, to relevant sections of NDA 21-160.

4 Pharmacology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

5 Pharmacokinetics/ADME/Toxicokinetics

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

6 General Toxicology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

7 Genetic Toxicology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

8 Carcinogenicity

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

9 Reproductive and Developmental Toxicology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

10 Special Toxicology Studies

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

11 Integrated Summary and Safety Evaluation

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission. The use of maltitol is approvable as an excipient in the liquid formulation of PhosLo® calcium acetate oral solution, a new dosage form of calcium acetate, which is already approved as two solid formulations: PhosLo® Tablets (NDA 19-976 approved 1990) and PhosLo® Gelcaps (NDA 21-160 approved 2001).

Literature database searches identified no studies describing the specific use of maltitol in patients with end-stage renal disease who require hemodialysis. However, maltitol is

currently a component of Nepro®, a nutritional supplement designed for patients with chronic kidney disease on dialysis (Stage 5). (b) (4) the use of liquid PhosLo® in combination with other diabetic food products and supplements containing maltitol is likely to increase this adverse event rate for gastrointestinal effects in the population of renal failure patients on dialysis. Although the maximum recommended dosage of liquid PhosLo® (90 mL per day or 18 gm of maltitol) is less than the threshold level of maltitol (30 gm) reported to induce a laxative effect, maltitol is used in many food products and nutritional supplements. Therefore, the labeling for liquid PhosLo® should indicate that liquid PhosLo® contains maltitol, which may induce laxative effects.

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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/

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

/s/

PATRICIA P HARLOW
03/15/2010

ALBERT F DEFELICE
03/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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Review Division:	Cardiovascular and Renal Products
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Template Version: December 7, 2009

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TABLE OF CONTENTS

Table of Tables

Table of Figures

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1.1.2 Additional Non Clinical Recommendations

None.

1.1.3 Labeling

Polyol sweeteners, like maltitol, have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. Although the maximum recommended dosage of liquid PhosLo® (90 mL per day or 18 gm of maltitol) is less than the threshold level of maltitol (30 gm) reported to induce laxative effects, maltitol is used in many food products and nutritional supplements, such as Nepro® designed specifically for patients with chronic kidney failure on dialysis. Therefore, the labeling for liquid PhosLo® should indicate that liquid PhosLo® contains maltitol, which may induce laxative effects.

1.2 Brief Discussion of Nonclinical Findings

Maltitol, a disaccharide sugar alcohol, is composed of glucose and sorbitol. In the intestine, maltitol is metabolized by disaccharidases to sorbitol and glucose which are then absorbed. At oral dosages less than 10 gm/kg, less than 2% of a maltitol dose is absorbed and excreted unchanged into the urine of normal rats and human subjects. After intravenous administration to rats, maltitol was excreted unchanged almost quantitatively into the urine within 1 hour. Maltitol induces an intermediate relative glucose response (RGR) compared to sucrose and sorbitol, because the rate of absorption of glucose from maltitol is slower than that of directly ingested glucose.

Maltitol and maltitol syrups are self-affirmed GRAS based on petition to the FDA. The European Union's Scientific Committee on Food (SCF) and the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) reviewed the safety data for maltitol at multiple meetings and concluded that maltitol is safe. The SCF and the JECFA assigned its safest category of an acceptable daily intake (ADI) for maltitol of "not specified."

Literature database searches identified no studies describing the specific use of orally administered maltitol in patients with renal impairment, renal insufficiency, chronic kidney disease, or in patients with end-stage renal disease who require hemodialysis. However, maltitol is thought to be dialyzable, since its molecular weight is 344. Furthermore, maltitol is a component of Nepro®, a nutritional supplement designed for patients with chronic kidney disease on dialysis (Stage 5).

Polyol bulk sweeteners, like maltitol, have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. Human tolerance studies indicate a laxative effect when maltitol is ingested at daily doses equal to or above 30-50 gm per day. Although the maximum recommended dosage of liquid PhosLo® (90 mL per day or 18 gm of maltitol) is less than the threshold level of maltitol (30 gm) reported to induce a laxative effect, maltitol is used in many food products and nutritional supplements, such as Nepro®. Therefore, the labeling for liquid PhosLo® should indicate that liquid PhosLo® contains maltitol, which may induce laxative effects.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

62-54-4

2.1.2 Generic Name

Calcium acetate, USP, oral solution

2.1.3 Code Name

Phoslyra™

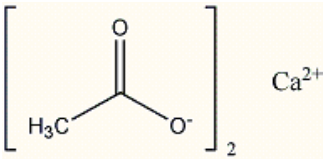
2.1.4 Chemical Name

Calcium acetate

2.1.5 Molecular Formula/Molecular Weight

Molecular Formula: $C_4H_6CaO_4$
Molecular Weight: 158.2

2.1.6 Structure



2.1.7 Pharmacologic class

Phoslyra™ calcium acetate oral solution is a phosphate binder.

2.2 Relevant IND/s, NDA/s, and DMF/s

Phoslyra™ calcium acetate oral solution is a new dosage form of calcium acetate a product already approved as two solid formulations: PhosLo® Tablets (NDA 19-976 approved 1990) and PhosLo® Gelcaps (NDA 21-160 approved 2001).

2.3 Clinical Formulation

2.3.1 Drug Formulation

The formulation for Phoslyra™ calcium acetate solution is summarized in Table 1 along with the daily intake of each of the solution components. Patients will take up to 30 mL of Phoslyra™ as a single dose three times per day. The maximum daily dose of Phoslyra™ results in the consumption of 12 grams of calcium acetate and 18 grams of maltitol.

Table 1: Reviewer's modification of Sponsor's Summary of the Phoslyra™ Formulation

Sponsor's table		Reviewer's addition	
Ingredient	Concentration per 5mL	Maximum amount per single dose	Maximum amount per day
Calcium Acetate USP	*667.0 mg/5mL	(b) (4)	(b) (4)
(b) (4) Maltitol NF	1000 mg/5mL		
Glycerin USP	(b) (4)		
Propylene Glycol USP			
Magnasweet 110			
Sucralose NF			
Methylparaben NF			
Povidone K25 USP			
Artificial Black Cherry Flavor (b) (4)			
Menthol Flavor, Natura (b) (4)			
Purified Water USP			
*On anhydrous basis			

2.3.2 Comments on Novel Excipients

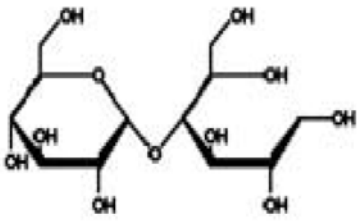
During the review process, questions were raised about the safety, absorption, excretion, and potential accumulation of one of the excipients, maltitol, in liquid PhosLo®. The reviewer's evaluation of maltitol summarized below is based on the reviewer's own literature searches and examination of the primary literature as well as the two following documents provided by the sponsor.

1. Maltitol Research Report prepared for Liquid PhosLo® telephone conference on January 31, 2008, NDA Module 1, Volume 1, Section 1.6.3, Attachment 2
2. Maltitol Research Report Responses to Questions from the FDA following the Liquid PhosLo® Telephone Conference on January 31, 2008), NDA Module 1, Volume 2, Section 1.6.3, Attachment 5.

Maltitol Background:

Maltitol (4-*O*-α-glucopyranosyl-D-sorbitol, CAS 585-88-6) is produced by the catalytic hydrogenation of maltose, which is a product of the hydrolysis of starch by beta-amylase. Maltitol is a disaccharide sugar alcohol that is not found in nature. A member of the polyols, maltitol (molecular weight 344) is composed of glucose and sorbitol as shown in Figure 1.

Figure 1: Structure of Maltitol



$C_{12}H_{24}O_{11}$ (4-o-α-D-glucopyranosil-D-sorbitol, 4-o-α-D- glucopyranosil-D-sorbitol, CAS registry number:585-88-6).

Maltitol is supplied as a crystalline powder (>98%) and as liquid syrups, often referred to as hydrogenated glucose syrups (HGS), that consist primarily of maltitol (50-90%) with lower proportions of sorbitol and hydrogenated oligo- and/or polysaccharides.

Safety of Maltitol:

Regulatory background

Maltitol and maltitol syrups are self-affirmed GRAS based on a petition entitled "To Affirm Generally Recognized As Safe (GRAS) Status of Maltitol As A Food Ingredient" by Towa Chemical Industry Co., Ltd., filed December 23, 1986 with the FDA (Kearsley and Deis, 2006). A determination of GRAS with or without petition to the FDA does not require FDA action. If a petition is submitted requesting GRAS affirmation and the petition is accepted for filing, the substance may be legally used for the petitioned uses

while awaiting FDA affirmation. The FDA has not indicated a need to designate an acceptable daily intake for maltitol. In addition, maltitol is specifically listed as an eligible noncariogenic carbohydrate sweetener that can be used to replace dietary sugars in CFR Title 21 Part 101 Food Labeling Subpart E 101.80, “Health claims: dietary noncariogenic carbohydrate sweeteners and dental caries.”

Maltitol and maltitol-based products (hydrogenated glucose syrups) were reviewed by the European Commission’s Scientific Committee on Food (SCF) in 1984 (Reports of the SCF, 1985). The SCF evaluated several studies conducted with a product containing 55% maltitol. These studies consisted of acute toxicity, subchronic toxicity in two species, a large number of mutagenicity tests, clinical tolerance studies and metabolic studies that included studies on metabolism of radiolabelled pure maltitol in rat and man. Based on these data and the data for sorbitol which along with glucose is a metabolic product of maltitol in rat and man, the Committee approved the use of maltitol-based products as acceptable with limitation due to their laxative action. During the re-evaluation of sweeteners in 1987 and 1988 the Committee made no changes to the previous evaluation of maltitol and maltitol-based products (Reports of the SCF, 1989).

The Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) reviewed the safety data for maltitol in hydrogenated glucose syrups at its 29th meeting (JECFA, WHO, 1986). Concluding that maltitol is safe, the JECFA assigned its safest category for maltitol of an acceptable daily intake (ADI) of "not specified," meaning that in the opinion of the Committee the total daily intake of maltitol arising from its use at the levels necessary to achieve the desired effect in food does not represent a hazard to health on the basis of the available data and no limits are placed on its use. Subsequently, the ADI of “not specified” for maltitol was confirmed at the 33rd meeting (JECFA, WHO, 1989), the 41st meeting (JECFA, WHO, 1993), and 49th meeting (JECFA, WHO, 1999).

Overview of Toxicology Studies with Maltitol

HGS or maltitol was evaluated in a series of assays that assess mutagenic potential. The JECFA evaluated unpublished study reports (summarized in Appendix 1) submitted to WHO by Roquette Freres (JECFA, WHO, 1986). HGS and maltitol powder were negative in all Ames assays using multiple bacterial strains with and without metabolic activation. Although HGS induced increases in responses in some *in vitro* studies using mammalian cells, it was considered negative in other mammalian cell assays. Importantly, no *in vivo* clastogenic or mutagenic effects were observed. The JECFA concluded that the weight of evidence indicates that HGS and maltitol are not genotoxic.

At the 29th meeting, the JECFA evaluated the submitted toxicity studies (JECFA, WHO, 1986) and concluded that HGS did not induce toxicologically significant effects. In acute toxicity studies, the LD_{50} values of single oral doses of HGS or maltitol were 16,000-24,370 mg/kg in mice and 24,000-24,370 mg/kg in rats. The JECFA concluded that HGS was not toxic in rats after prolonged feeding of up to 15-20% of the diet in 13-week subchronic toxicity studies. HGS also produced no adverse effects, except for diarrhea, in dogs receiving repeated oral administration of 4.95 grams/kg/day in a 90-day study.

In a 24-month study, Sprague Dawley rats received HGS in drinking water at a level of 18% (w/v). Although HGS did not induce overt signs of toxicity, some treatment-related changes were observed. The findings included increased water consumption and decrease in the electrolyte concentrations in the urine, a transient initial period of increased incidence of diarrhea and cecum enlargement of the HGS-treated animals. The two later findings were attributed to adaptive physiological responses to the treatment with high concentrations of slowly digestible carbohydrates, such as polyols. Importantly, HGS did not induce an increased incidence of tumors (Dupas et al 1982).

In an adequate teratogenicity study (Dupas & Siou, 1985), HGS was administered orally at dosage levels of 0, 3000, 5000, or 7000 mg/kg/day to 30 pregnant Sprague-Dawley rats/group from day 6 to day 15 of gestation, inclusive. On day 20 of gestation no adverse effects were observed on pregnant females or on litter responses (litter size, fetal weight, or pre- and post-implantation losses). Fetal examination indicated no visceral malformations, no major skeletal malformations and no differences in degree of bone ossification, while any minor skeletal malformations observed were not dose related.

At the same meeting, the JECFA also evaluated a multigeneration reproduction study in Sprague-Dawley rats, in which HGS was administered in drinking water as an 18% aqueous solution (dry weight/volume). Males received 5.4-8.5 g HGS per day and females received 5.3-13.5 g HGS per day for 3 successive generations. No adverse effects were observed on adult survival rates, hematological parameters of parental generations, fertility, fecundity, or postnatal survival compared to control animals. No treatment-related effects were noted in morphological observations of pups and adult animals. However, treated pups at weaning had slight reductions in average body weights that were still within the normal range for the strain. Although relative kidney weights of some HSH-treated males were lower than those of control animals and the relative cecum weights of some HSH-treated males and females were higher than those of concurrent controls, all other parameters were not affected by treatment (Leroy & Dupas, 1983).

Modderman (1993) published the data from the three above studies that were also submitted to the FDA as part of a GRAS affirmation request (GRASP 3G0286) for a product produced by Roquette Freres Corporation. Modderman concluded that the NOAEL for HSG in the 24-month study and the multi-generational study was greater than the 18% tested in these studies. In addition, he concluded that HSG induced no significant teratological effects in male or females and the NOAEL was greater than 7 gm/kg.

At the 41st meeting, the JECFA evaluated unpublished study reports for a 52-week chronic study and a 106-week carcinogenicity study of crystalline maltitol which was administered as dosages of 0, 0.5, 1.5 and 4.5 gm/kg/d in the diet to Sprague Dawley in rats (JECFA, WHO, 1993). No adverse effects were observed in the toxicity study. In the carcinogenicity study, a slightly increased incidence of mammary gland adenocarcinomas was observed in female rats at doses of 1.5 and 4.5 g/kg/day. Since these incidences were within the range reported in the historical control and increased incidences of mammary gland adenomas or fibroadenomas were not observed, the JECFA did not consider the increase in mammary gland adenocarcinomas to be related

to treatment. Histopathological changes related to treatment were observed in the adrenal gland and included increased incidences of both benign and malignant pheochromocytomas in male and female rats in the high-dose group and an increased incidence of slight to moderate adrenal medullary hyperplasia in all treated groups. However, the JECFA noted that adrenal medullary lesions in rats previously were associated with high intake levels of several other poorly-absorbed polyols. Although the JECFA recommended that the mechanisms and the toxicological significance of the appearance of pheochromocytomas associated with polyols and other poorly-absorbed carbohydrates be investigated, the JECFA confirmed the ADI "not specified" for maltitol and maltitol syrup.

A review by Lynch et al (1996) addressed the significance of the adrenal proliferative lesions induced in the rat by poorly digestible carbohydrates. In chronic rat studies, adrenal medullary tumors developed in response to high dietary concentrations of some polyols, including maltitol, only after long-term treatment and only at high doses, generally >5% of the diet. Adrenal medullary lesions are not observed in long-term studies in mice or dogs that received similar doses of polyols. In rats fed diets containing high concentrations of polyols, hypercalciuria occurs in a dose-related manner resulting from increased calcium absorption (Fournier et al 1967; Hämäläinen et al 1985; Amman et al 1988; Goda et al 1992; Brommage et al 1993) probably due to changes in the membrane permeability of the intestinal epithelium brought about by the increased osmotic pressure of the intestinal contents (Pansu et al., 1975; Hämäläinen and Makinen, 1989; Langkilde et al., 1994). Hypercalciuria in rats has been associated with the increased incidence of adrenal medullary hyperplasia/neoplasia (Bär, 1986). However, hypercalciuria resulting from increased absorption does not occur to any significant extent in humans ingesting even up to 100 g of individual polyols per day (Mäkinen et al., 1981). The rat is uniquely sensitive to the development of these adrenal medullary proliferative lesions, whereas other species like the mouse are resistant. Based on the species specificity of the response of the rat adrenal medulla and the species-specific nature of the mode of action, Lynch et al (1996) concluded the rat adrenal medullary lesions appear to be a species-specific phenomenon, probably due to alterations of calcium homeostasis, and are irrelevant to humans.

Absorption, Metabolism, and Excretion of Maltitol

At its 29th meeting (JECFA, WHO, 1986), the JECFA also reviewed a large number of metabolism studies for maltitol in hydrogenated glucose syrups. These studies are summarized in Appendix 2.

The JECFA concluded that after oral ingestion maltitol is hydrolyzed by disaccharidases into glucose and sorbitol in the gastrointestinal tract primarily by intestinal flora. Sorbitol is absorbed very slowly, while glucose is readily absorbed by the mammalian body. However, the rate of absorption of glucose from maltitol is slower than that of directly ingested glucose, because maltitol hydrolysis is slow and sorbitol inhibits the absorption of glucose.

Some absorption of maltitol itself was detected in some studies but it was quickly excreted unchanged in the urine. Absorption amounts of maltitol vary in different studies depending on the measurement made and the dosages of maltitol administered.

However, the review by Livesey (2003) states that a maximum of 2% of maltitol is absorbed and excreted unchanged in the urine. In rats, Lian-Loh et al (1982) found less than 1% of an oral maltitol dose in urine of normal rats when the dosage was 10 gm/kg or less (Table 2). However, when germ-free rats received maltitol or when normal rats received dosages above 10 gm/kg, the percentage of the oral maltitol dose increased to 9 to 11%, indicating a saturation of the disaccharidases that hydrolyze maltitol. In these experiments, the levels of sorbitol in the urine were equal to or greater than the levels of unchanged maltitol and less than 1% of the maltitol dose was excreted unchanged into the feces even in the germ-free rats. After intravenous administration to rats, maltitol was excreted unchanged almost quantitatively (88%) in the urine within 1 hour, producing no significant rise in blood glucose. The summaries of the nonclinical studies using oral administration of maltitol do not indicate accumulation of maltitol in the plasma or tissues of healthy animals. A study in humans (Secchi et al 1986) also showed a very low absorption of maltitol itself (1.3%) when maltitol was administered at a daily dose of 30 gm. Since the daily dose of maltitol from liquid PhosLo® is 90 mL per day or 18 gm of maltitol, less than 2% of maltitol itself is expected to be absorbed.

Table 2: Urinary Excretion of Unchanged Maltitol

		Dose		Unchanged maltitol in urine	
Reference	**Species**	**Total/day**	**gm/kg/day**	**mg/24 hr**	**% of dose**
Lian-Loh et al, 1982	Rat, normal	1 gm	4	4	0.2%
	Rat, normal	2 gm	13	180	9%
	Rat, normal	2 gm	10	10	0.5%
	Rat, germ-free	2 gm	10	212	10.6%
Secchi et al, 1986	Human	3 X 10 gm	0.5	350-400	1.2-1.3%
Adapted from Dills (1989)					

In humans, maltitol is less glycemic than glucose when given to non diabetic subjects, non-insulin dependent diabetic (NIDDM) subjects, and insulin-dependent (IDDM) subjects due to the slower release of glucose from HGS compared to directly ingested glucose, which is rapidly absorbed in the small intestine. Maltitol is generally well tolerated by human volunteers and there were no effects on clinical chemistry or hematological parameters, including glycemia in either diabetic or nondiabetic subjects (Livesey, 2003).

Studies in animals and humans revealed that HGS and its major component maltitol produced significantly lower blood-glucose levels and more stable insulin levels than glucose or sucrose due to slow metabolism of maltitol. Livesey (2003) summarized the human studies using a wide range of intakes (10 to 70 g) of maltitol syrups in addition to other polyols in Type 1 and Type 2 diabetic patients in addition to normal subjects. Table 3 summarizes these human studies and shows that maltitol has an intermediate relative glucose response (RGR) compared to sucrose and sorbitol.

Table 3: Reviewer's Summary of Studies Evaluating Relative Glucose Response (RGR) from Table 4 in Livesey (2003)

Compound	Reference	Subjects	Subject N/study	Number of Studies	Mean RGR	Range RGR
Sucrose	Glucose	Normal	8-12	10	69	58-89
		Diabetic	6-8	2	84	79-89
Maltitol	Glucose	Normal	6-19	6	36	25-49
		Diabetic	6-21	3	34	25-39
Sorbitol	Glucose	Normal	2-9	7	8.7	3-14
		Diabetic	11-21	3	9.6	4-14

However, polyol bulk sweeteners, like maltitol, have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. Human tolerance studies indicate a laxative effect when maltitol is ingested above 30-50 gm per day. Grabitske and Slavin (2009) reviewed the gastrointestinal effects of low digestible carbohydrates, including six primary studies evaluating effects associated with maltitol consumption (Beaugerie et al. 1990; Koizumi et al 1983a; Koutsou et al 1996; Ruskoné-Fourmestraux et al 2003; Storey et al1998; Zunft et al1983). These studies indicate threshold amounts for maltitol based on gastrointestinal effects are 30–40 g maltitol as a single dose and 35-57 g maltitol as divided daily amounts over a period of more than one week. The findings indicate that even single intakes up to 40 g maltitol per day may be generally well-tolerated in un-adapted individuals. Higher daily intakes may be tolerated if the total amount is divided throughout the day and gradually increased over time. However, intakes above 60-70 g/day induced diarrhea in most individuals. The authors recommended that daily amounts of up to 30 to 40 g maltitol should be acceptable to most people.

The sponsor states that most patients will require 45 to 60 mL of liquid PhosLo® per day and hence will consume 9 to 12 gm of maltitol per day. The maximum recommended dosage of liquid PhosLo® is 90 mL per day or 18 gm of maltitol. The maximum daily dosage level (18 gm) of maltitol from liquid PhosLo® is less than the threshold level of maltitol (30 gm) reported to induced laxative effects. However, the maximum daily dosage level (18 gm) of maltitol in liquid PhosLo® is above the threshold level (10 g) set by the European Commission's Guidelines on the labeling of excipients in the label of medicinal products for human use (CPMP/463/00, July 2003). The lower threshold set by the European Commission's Guidelines is appropriate because maltitol is used in many food products, such as baked goods, dairy products, beverages, confections, and chocolate as well as dietary and diabetic products. For example, one Glucerna snack bar contains 10 gm maltitol per bar. Depending upon the foods consumed, an individual could easily consume more than 30 g maltitol per day which could induce laxative effects.

Table 4: Guidelines for Maltitol Labeling (CPMP/463/00, July 2003)

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Maltitol E965 and Isomaltitol E953, Maltitol Liquid (see Hydrogenated Glucose Syrup)	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	(b) (4) proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
		10 g	May have a mild laxative effect Calorific value 2.3 kcal/g maltitol (or isomaltitol)	

Use of Maltitol in Other Drug Products

The FDA "Inactive Ingredient list for Approved Products" (last updated January 13, 2010) indicates that maltitol is approved for oral administration in solution at a maximum potency of 65% (w/v). In contrast, PhosLo contains 20% maltitol (w/v).

Use of maltitol in the indicated population

The sponsor's and reviewer's literature database searches identified no studies describing the specific use of orally administered maltitol in patients with renal impairment, renal insufficiency, chronic kidney disease, or in patients with end-stage renal disease who require hemodialysis. However, maltitol is thought to be dialyzable, since its molecular weight is 344.

One nutritional supplement, Nepro® with Carb Steady®, containing maltitol is designed specifically for patients with chronic kidney disease on dialysis (Stage 5). One can of Nepro® contains (b) (4) of maltitol. Consumption of three cans of Nepro® per day results in a daily intake of (b) (4) maltitol per day. Patients that are tube fed a typical diet of 1,800 calories of Nepro® consume (b) (4) maltitol per day. The use of liquid PhosLo® in combination with Nepro® and other diabetic food products containing maltitol is likely to induce adverse gastrointestinal effects.

The reviewer notes the following publication relevant to the use of maltitol.

Maltitol has been evaluated as an osmotic agent for peritoneal dialysis (Tomo et al 2000) relative of other saccharides. In contrast to glucose, no increases in furosine- or N-(carboxymethyl)-lysine were seen *in vitro* after 3 and 6 weeks of incubation of maltitol with bovine serum albumin indicating that maltitol did not induce advanced glycation end-product (AGE) formation. An *in vivo* study in Sprague Dawley rats showed that the quantity of abdominal fluid after 2-, 4- and 6-hour dwell times for maltitol were equal to or greater than the quantity of abdominal fluid after the same dwell times for glucose. No differences in dialysate-to-plasma ratios for urea nitrogen or creatinine were seen in any group. The authors concluded that AGE formation in peritoneal tissue might be reduced by using saccharides such as maltitol with a modified carbonyl group as osmotic agents for peritoneal dialysates.

Comments on the results of bioequivalence study LP-RTG-01-01

To support NDA 22581, the sponsor provided the results of a bioequivalence study (LP-RTG-01-01) in healthy volunteers comparing liquid PhosLo Oral Solution to the previously approved PhosLo Gelcaps. The randomized, controlled, open label study involved three cross-over periods in which either liquid PhosLo Oral Solution (30 mL t.i.d.) or PhosLo Gelcaps (6 gelcaps t.i.d.) or calcium citrate (5 caplets) as a positive control was administered. The study report indicates that the serum glucose and insulin levels and patterns were comparable between calcium acetate oral solution and PhosLo Gelcaps and calcium citrate. These data, summarized in Appendix 3, indicate no significant influence of the maltitol in the oral solution on serum glucose control. The sponsor reported that the insulin levels demonstrated troughs between meals and postprandial peaks, indicating typical insulinemic responses, although ranges varied widely. In addition, one subject exhibited hyperglycemia in one instance (2-hour postprandial serum glucose >140 mg/dL) and several subjects exhibited mild hypoglycemia (serum glucose <65 mg/dL) at repeated time points.

In both the liquid PhosLo® and the PhosLo® Gelcaps treatment groups, the most common adverse events were gastrointestinal symptoms with mild, transient diarrhea that was more common in the liquid PhosLo® treatment group than in the other treatment groups. The adverse gastrointestinal events with the liquid PhosLo® may have resulted from the 18 gm of maltitol in the liquid PhosLo® formulation.

2.3.3 Comments on Impurities/Degradants of Concern

Not applicable.

2.4 Proposed Clinical Population and Dosing Regimen

Patients with end stage renal disease will take the liquid formulation of Phoslyra™ with meals three times a day.

2.5 Regulatory Background

Phoslyra™ calcium acetate oral solution (liquid PhosLo®) is a new dosage form of calcium acetate which is already approved as two solid formulations. PhosLo® Tablets were approved in 1990 under NDA 19-976 and PhosLo® Gelcaps were approved in 2001 under NDA 21-160.

3 Studies Submitted

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission. The sponsor referred to NDA 19-976 Volume 1.2 Section 314.50 d(2) Nonclinical Pharmacology and Toxicology for Module 4 Nonclinical Study Reports and, if necessary, to relevant sections of NDA 21-160.

4 Pharmacology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

5 Pharmacokinetics/ADME/Toxicokinetics

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

6 General Toxicology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

7 Genetic Toxicology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

8 Carcinogenicity

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

9 Reproductive and Developmental Toxicology

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

10 Special Toxicology Studies

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission.

11 Integrated Summary and Safety Evaluation

No nonclinical study of the drug substance, calcium acetate, was included in the NDA 22-581 submission. The use of maltitol is approvable as an excipient in the liquid formulation of PhosLo® calcium acetate oral solution, a new dosage form of calcium acetate, which is already approved as two solid formulations: PhosLo® Tablets (NDA 19-976 approved 1990) and PhosLo® Gelcaps (NDA 21-160 approved 2001).

Maltitol, a disaccharide sugar alcohol, is composed of glucose and sorbitol. In the intestine, maltitol is metabolized by disaccharidases to sorbitol and glucose which are

then absorbed. At oral dosages less than 10 gm/kg, less than 2% of a maltitol dose is absorbed and excreted unchanged into the urine of normal rats and human subjects. After intravenous administration to rats, maltitol was excreted unchanged almost quantitatively into the urine within 1 hour. Maltitol induces an intermediate relative glucose response (RGR) compared to sucrose and sorbitol, because the rate of absorption of glucose from maltitol is slower than that of directly ingested glucose.

Maltitol and maltitol syrups are self-affirmed GRAS based on petition to the FDA. The European Union's Scientific Committee on Food (SCF) and the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) reviewed the safety data for maltitol at multiple meetings. The studies evaluated included multiple genotoxicity studies and acute, subchronic and chronic toxicity studies in mice, rats and dogs as well as an embryo-fetal development study, a multi-generation reproduction/development study and two-year carcinogenicity studies in rats. Concluding that maltitol is safe, the SCF and the JECFA assigned its safest category of an acceptable daily intake (ADI) for maltitol of "not specified."

Literature database searches identified no studies describing the specific use of orally administered maltitol in patients with renal impairment, renal insufficiency, chronic kidney disease, or in patients with end-stage renal disease who require hemodialysis. However, maltitol is thought to be dialyzable, since its molecular weight is 344. Furthermore, maltitol is a component of Nepro®, a nutritional supplement designed for patients with chronic kidney disease on dialysis (Stage 5).

Polyol bulk sweeteners, like maltitol, have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. Human tolerance studies indicate a laxative effect when maltitol is ingested at daily doses equal to or above 30-50 gm per day. Although the maximum recommended dosage of liquid PhosLo® (90 mL per day or 18 gm of maltitol) is less than the threshold level of maltitol (30 gm) reported to induce a laxative effect, maltitol is used in many food products and nutritional supplements, such as Nepro®. Therefore, the labeling for liquid PhosLo® should indicate that liquid PhosLo® contains maltitol, which may induce laxative effects.

12 Appendix/Attachments

Appendix 1: Maltitol Genetic Toxicity Results

Assay Description	Doses	Result	Reference
Ames test with five Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, or TA1538 with and without metabolic activation	HGS at concentrations of 0.5 to 1000 µg/plate	Negative	Mondino et al., 1979b
Ames assay with five Salmonella typhimurium strains (TA98, TA100, TA1535, TA1537, TA1538) or Escherichia coli WP2/pKM101. *In vivo* micronucleus test in bone marrow after oral administration to mice	HGS and maltitol powder, Ames: 0.5-50 mg per plate with and without rat liver S9 mix. Micronucleus: at 3.75-30 g per kg	Ames: Negative Micronucleus: negative	Takizawa and Hachiya, 1984
Four strains of Salmonella typhimurium with or without activation by rat liver microsomes	0.01 to 1 ml/plate (0.2-20 mg),	Negative	Fouillet et al., 1978a; 1978b; Hofnung, 1978
Urine collected on day 15 from male Sprague-Dawley rats (8/group, 4 controls) was assayed for mutagenic activity against five Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 with or without metabolic activation.	Daily gavage doses of HGS equivalent to 0, 2.5, 5, 10, 15, or 20% in the diet for 15 days.	Negative	Farrow, 1982d
In vivo micronucleus test using adult male mice after oral administration	HGS doses of 10 or 50 ml/kg for 2 days.	Negative	Siou et al., 1981
Incorporation of ^{3}H-thymidine into human heteroploid fibroblasts	HGS up to 300 µg/ml	Negative	Mondino, 1980
Induction of forward mutations at the thymidine kinase locus in the L5178Y mouse lymphoma cell line	HGS from 27 to 1000 µg/ml with and without metabolic activation	Slight increase in mutation frequency, but not dose-related	Farrow, 1982b
In vitro transformation assay using C3H/10T 1/2 (Clone 8) mouse fibroblast cells	HGS from 10-1000 µg/ml with and without metabolic activation	Significant increase in number of transformed foci	Farrow & Sernau, 1982; Farrow, 1982c
Chromosomal aberration in Chinese hamster ovary cells *in vitro*	HGS from 49 to 4900 µg/ml with or without metabolic activation.	Negative	Farrow, 1982a
Schizosaccharomyces pombe strain in a host-mediated assay using mice	1 gm/kg	Negative	Mondino et al., 1979a
Sister chromatid exchange (SCE), chromosome aberration (CA), and micronucleus formation (MN) in human peripheral lymphocytes at 24 hr and 48 hr *in vitro*. [Note: Since negative control data for the 48 hour timepoint and laboratory historical data were not provided, the results of this study cannot be adequately interpreted.	Maltitol powder at 1.25, 2.5, 5 mg/mL	SCE: negative CA: Significant increase at 24 hr, but not 48 hr – not dose-related MN: Significant increase at 24 and 48 hr, but not dose-related	Canimoglu and Rencüzogullari 2006.

Appendix 2: Summary of Maltitol Metabolism Studies from JECFA (1986)

Study results	Reference
Animal studies	
Single oral dose of ^{14}C- maltitol in mice. Glucose and sorbitol, but not maltitol, were detected in the blood of treated mice.	Kamoi, 1975
Single oral dose of up to 600 mg maltitol to SD rats - Only a small quantity of non-hydrolysed maltitol crossed the intestinal barrier, since its concentration in blood was very small. Urinary excretion of sorbitol, maltitol, or HGS accounted for about 1% of the ingested quantity over a 7-hour period.	Verwaerde & Dupas, 1982a
Two sets (control and treated) of Sprague-Dawley rats treated with HGS (18% W/V) for 10 days, and then water until sacrifice. One set sacrificed on day 11; the other set sacrificed on day 21. After maltitol ingestion per day ranging from 2.97-4.27 g in males and 2.46-3.03 g/day in females, the maximum quantity of maltitol excreted per day in urine was 6.27 ± 4.50 mg (0.14%) and 2.04 ± 1.2 mg (0.09%), respectively. The ingestion of HGS resulted in very small quantities of maltitol in the urine and maltitol was not detected in plasma.	Verwaerde & Dupas, 1982b
Groups of Wistar rats received 1.2 ml of a 50%-aqueous solution of maltitol, xylitol, sorbitol, or glucose orally. Measurement of blood glucose hourly for 6 consecutive hours indicated the animals given the sugar alcohols exhibited lower blood glucose values than animals receiving glucose itself. Maltitol disappeared from the digestive tract the quickest.	Takai et al 1972.
Wistar rats receiving 13 or 26% maltitol for 9 weeks had reduced body-weight gains and increased intestinal weights as compared with controls. Neither maltitol dehydrogenase nor sorbitol dehydrogenase was induced.	Inoue, 1970
Maltitol was administered to rats either orally at a dosage of 2 g/kg or intravenously at a dosage of 1 g/kg. At 4.5 hours post dose, maltitol induced hyperglycemia similar to that observed by the administration of an equivalent amount of glucose or sucrose. [Note: not clear whether this effect was observed for both oral and iv administration]	Lederer et al., 1974
Fasted germ-free or normal rats received 10 gm maltitol orally. Urine and faeces collected for 24 hours after dosing showed no detectable glucose for of any of the animals. Although no significant difference was found for the maltitol content of the urine, the sorbitol content of the urine was higher in germ-free than in normal animals. Normal animals utilized 96% of the maltitol, while germ-free animals utilized 84%, indicating that microbial utilization is a minor factor in maltitol metabolism. Maltitol injected i.v. (0.25 g/animal) was excreted almost quantitatively (88%) in the urine, producing no significant rise in blood glucose. No sorbitol was detected in the blood. The small amount of sorbitol in the urine indicated slight utilization of maltitol in body tissues	Kearsley et al., 1982 Stärche, 34, 279-283.
Rats received a single oral dose of 1 or 2 g maltitol. Although very little of either maltitol or sorbitol appeared in the feces, appreciable amounts of sorbitol were found in the urine indicating maltitol hydrolysis. The quantities of both maltitol and sorbitol in the urine were significantly higher when HGS was administered.	Lian-Loh et al., 1982
Excretion of maltitol and sorbitol were compared in germ-free and normal rats given oral doses of 2 g maltitol. Although significantly less of maltitol and sorbitol was recovered in the feces of normal rats, urinary excretion was similar in both groups. Rats injected with maltitol (250 mg/animal) cleared virtually all from the blood within 1 hour, and showed no evidence of a rise in blood glucose after injection of maltitol. Little or no metabolism of maltitol had occurred in the tissues; maltitol hydrolysis is catalyzed by gastric or intestinal enzymes.	Lian-Loh et al., 1982

Fed and fasted Wistar rats were dosed orally with 320 mg/kg, containing ^{14}C-maltitol. About 22 and 33% of the dosed maltitol was hydrolysed in the fed and fasted group, respectively. Excretion in the urine of 14C-derivatives was more rapid in the fasted group than in the fed group. About 50 and 34% of the ^{14}C- excreted in the urine was maltitol in the fasted and fed group, respectively. A portion of the administered maltitol was not metabolized, but was absorbed in the intestinal tract and quickly excreted in the urine	Oku et al., 1981.
Rats orally dosed with radioactive maltitol solution showed a rapid (1-2 hours) and appreciable appearance of 14CO2 (45.5% in 14 hours). Calculated caloric utilization was 76%. Radioactivity in the urine varied from 3.94 to 9.40% and the feces contained 4.38-13.22% of the ingested radioactivity at 72 hours.	Rennhard & Bianchine, 1975).
After oral administration of HGS or maltitol (400 mg) to rats, the results showed that the alpha-1,4 glucose-sorbitol linkage was hydrolysed in rats, whether fasted or not. Sorbitol from the hydrolysis of maltitol or HGS was more rapidly absorbed by fed rats than by fasted rats. However, maltitol or sorbitol urinary excretion was not affected..	Verwaerde & Dupas, 1984
Two male beagle dogs given 14C-maltitol orally had 7.8 and 3.8% of the administered radioactive dose in the urine after 48 hours	Rennhard & Bianchine, 1975.
Human studies	
Six fasted normal volunteers and 4 diabetics received oral doses of 30 g maltitol or sucrose, and at 0.5-, 1-, 1.5-, 2-, and 3-hours post-dosing the glucose and maltitol concentrations in blood and urine were analysed. Maltitol administration induced lower blood glucose levels than the sucrose administration, both in normal and diabetic volunteers. Urinary excretion of maltitol was also low,	Atsuji et al., 1982
Three normal volunteers, 3 diabetics, and 1 subject with acute hepatitis, received oral doses of 50 g of glucose, sorbitol, or maltitol in aqueous solution, and at 0-, 0.5-, 1-, 2-, and 3-hours post dosing the blood concentrations of these sugars were measured. Maltitol concentrations peaked at 0.5 hour and decreased sharply thereafter. Glucose followed a similar pattern, but its concentration was significantly higher than maltitol, especially in diabetics.	Nishikawa, 1982
Nine diabetics received a single oral dose of 50 g maltitol, 50 g glucose, or 7 consecutive daily doses of 50 g each of sucrose, powdered starch syrup, or maltitol. At 0, 1, 2, and 3 hours post-administration, single doses of maltitol produced lower blood glucose and immuno-reactive insulin (IRI) levels but higher free fatty acids (FFA), and triglycerides (TG) concentrations than glucose alone. The results from the multiple administrations were unclear.	Takeuchi & Yamashita, 1972.
Five fasted normal men ingested 0.5 g/kg/day maltitol for 30 consecutive days. On days 1, 7, and 30 at 1, 2, and 3 hours after the daily administration of maltitol, the concentrations of maltitol and glucose in the blood were measured along with other clinical chemistry values (BUN). In 3 volunteers, blood glucose levels increased by about 20% 1 hour after maltitol administration. No other changes were observed	Itoya et al., 1974.
Six male subjects were placed on a diet containing 40% carbohydrate (160 gm/day) and 60% protein for 10 days. The carbohydrate in the diet consisted of HGS, high-maltitol syrup, 43% glucose syrup, or glucose (the standard). The results of blood glucose and serum insulin analyses indicate that prolonged consumption of high-maltitol syrup or HGS leads to some adaption to these compounds as judged by elevated blood glucose and insulin peak values at the end of the trial. Subjects ingesting HGS or high-maltitol syrup excreted up to 10 g sorbitol and 0.5 g maltitol in the urine. [Unclear what was being measured]	Kearsley et al., 1982

Appendix 3: Sponsor's Summary of Glucose and Insulin Data in Bioequivalence Study LP-RTG-01-01

Matrix	Geometric Mean		Ratio (%)[a]	90% CI[b]	
Dependent Variable, n	Test Gelcap	Reference Citrate	(Test/Reference)	Lower	Upper
Liquid PhosLo® versus Calcium Citrate					
12. Serum Glucose, Day 3					
C_{max}, n = 36	114.54	115.59	99.10	94.05	104.42
$AUC_{(0-6)}$, n = 36	523.13	519.48	100.70	98.11	103.36
13. Serum Insulin, Day 3					
C_{max}, n = 36	44.179	54.087	81.68	66.33	100.59
$AUC_{(0-6)}$, n = 36	111.43	126.23	88.28	72.77	107.08
PhosLo® Gelcap versus Calcium Citrate					
2. Serum Glucose, Day 3					
C_{max}, n = 36	120.42	115.59	104.18	98.87	109.77
$AUC_{(0-6)}$, n = 36	527.32	519.48	101.51	98.90	104.19
3. Serum Insulin, Day 3					
C_{max}, n = 36	53.398	54.087	98.73	80.17	121.58
$AUC_{(0-6)}$, n = 36	129.30	126.23	102.43	84.45	124.25

Liquid PhosLo® versus PhosLo® Gelcap – Serum Glucose

Parameter	C_{max} (mg/dL) (n=36)		AUC_{0-6} (hr*mg/dL) (n=36)		Average Conc. (mg/dL) (n=36)	
Treatment	Liquid PhosLo (A)	PhosLo Gelcap (B)	Liquid PhosLo (A)	PhosLo Gelcap (B)	Liquid PhosLo (A)	PhosLo Gelcap (B)
Geometric LS mean, unadjusted	114.54	120.42	523.13	527.32	87.63	87.67
Ratio (A)/(B) (in %)	95.12		99.21		99.95	
90% CI	(90.28, 100.23)		(96.65, 101.82)		(97.25, 102.73)	

Liquid PhosLo® versus PhosLo® Gelcap – Serum Insulin

Parameter	C_{max} (mU/L) (n=36)		AUC_{0-6} (hr*mU/L) (n=36)		Ave. Conc. (mU/L) (n=36)	
Treatment	Liquid PhosLo (A)	PhosLo Gelcap (B)	Liquid PhosLo (A)	PhosLo Gelcap (B)	Liquid PhosLo (A)	PhosLo Gelcap (B)
Geometric LS mean, unadjusted	44.179	53.398	111.43	129.30	18.37	20.73
Ratio (A)/(B) (in %)	82.73		86.18		88.65	
90% CI	(67.18, 101.88)		(71.04, 104.53)		(73.55, 106.85)	

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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/

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03/11/2010

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03/12/2010