



NDA 021160/S-015

SUPPLEMENT APPROVAL

Fresenius Medical Care North America
Attention: Nancy Grigoriadis
Sr. Regulatory Affairs Specialist
920 Winter Street
Waltham, MA 02451-1457

Dear Ms. Grigoriadis:

Please refer to your Supplemental New Drug Application (sNDA) dated October 1, 2010, received October 4, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PhosLo (calcium acetate) 667 mg Gelcaps.

This “Prior Approval” supplemental new drug application provides for the conversion of the label to the Physician Labeling Rule (PLR) format; specific content changes are as follows:

1. Under **INDICATIONS AND USAGE**, the first paragraph was changed from:

PhosLo is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

To:

PhosLo[®] is a phosphate binder indicated to reduce serum phosphorus in patients with end stage renal disease (ESRD).

2. Under **DOSAGE AND ADMINISTRATION**, the sentence “Increase the dose gradually to lower serum phosphate levels to the target range, was added to the first paragraph. The paragraph now reads:

The recommended initial dose of PhosLo[®] for the adult dialysis patient is 2 gelcaps with each meal. Increased the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Most patients require 3-4 gelcaps with each meal.

3. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

Patients with end stage renal failure may develop hypercalcemia when given calcium with meals. No other calcium supplements should be given concurrently

with PhosLo. Progressive hypercalcemia due to overdose of PhosLo may be severe as to require emergency measures. Chronic hypercalcemia may lead to vascular calcification, and other soft-tissue calcification. The serum calcium level should be monitored twice weekly during the early dose adjustment period. **The serum calcium times phosphate(CaXP) product should not be allowed to exceed 66.**

Radiographic evaluation of suspect anatomical region may be helpful in early detection of soft tissue calcification.

Excessive dosage of PhosLo induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. PhosLo should not be given to patients on digitalis, because hypercalcemia may precipitate cardiac arrhythmias. PhosLo therapy should always be started at low dose and should not be increased without careful monitoring of serum calcium. An estimate of daily calcium intake should be made initially and the intake adjusted as needed. Serum phosphorus should also be determined periodically.

To:

Patients with end stage renal disease may develop hypercalcemia when treated with calcium, including calcium acetate (PhosLo). Avoid the use of calcium supplements, including calcium-based nonprescription antacids, concurrently with PhosLo[®].

An overdose of PhosLo may lead to progressive hypercalcemia, which may require emergency measures. Therefore, early in the treatment phase during the dosage adjustment period, monitor serum calcium levels twice weekly. Should hypercalcemia develop, reduce the PhosLo[®] dosage, or discontinue the treatment, depending on the severity of hypercalcemia.

More severe hypercalcemia (Ca >12 mg/dL) is associated with confusion, delirium, stupor and coma. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing PhosLo[®] therapy.

Mild hypercalcemia (10.5 to 11.9 mg/dL) may be asymptomatic or manifest as constipation, anorexia, nausea, and vomiting. Mild hypercalcemia is usually controlled by reducing the PhosLo[®] dose or temporarily discontinuing therapy. Decreasing or discontinuing Vitamin D therapy is recommended as well.

Chronic hypercalcemia may lead to vascular calcification and other soft-tissue calcification. Radiographic evaluation of suspected anatomical regions may be helpful in early detection of soft tissue calcification. The long term effect of

PhosLo[®] on the progression of vascular or soft tissue calcification has not been determined.

Hypercalcemia (>11 mg/dL) was reported in 16% of patients in a 3-month study of solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment.

Maintain the serum calcium-phosphorus (Ca x P) product below 55 mg²/dL².

4. Under **WARNINGS AND PRECAUTIONS**, a new section was added. The section reads:

5.2 Concomitant Use with Medications

Hypercalcemia may aggravate digitalis toxicity.

5. Under **ADVERSE REACTIONS**, the section was changed from:

In clinical studies, patients have occasionally experienced nausea during PhosLo therapy. Hypercalcemia may occur during treatment with PhosLo. Mild hypercalcemia (Ca>10.5mg/dl) may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting. More severe hypercalcemia (Ca>12mg/dl) is associated with confusion, delirium, stupor and coma. Mild hypercalcemia is easily controlled by reducing the PhosLo dose or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing PhosLo therapy. Decreasing dialysate calcium concentration could reduce the incidence and severity of PhosLo induced hypercalcemia. The long-term effect of PhosLo on the progression of vascular or soft tissue calcification has not been determined. Isolated cases of pruritus have been reported which may represent allergic reactions.

To:

Hypercalcemia is discussed elsewhere [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical studies, calcium acetate has been generally well tolerated.

PhosLo[®] was studied in a 3-month, open-label, non-randomized study of 98 enrolled ESRD hemodialysis patients and an alternate liquid formulation of calcium acetate was studied in a two week double-blind, placebo-controlled,

cross-over study with 69 enrolled ESRD hemodialysis patients. Adverse reactions (>2% on treatment) from these trials are presented in Table 1.

Table 1: Adverse Reactions in Patients with End-Stage Renal Disease Undergoing Hemodialysis

Preferred Term	Total adverse reactions reported for calcium acetate n=167 n (%)	3-mo, open-label study of calcium acetate n=98 n (%)	Double blind, placebo-controlled, cross-over study of liquid calcium acetate n=69	
			Calcium acetate n (%)	Placebo n (%)
Nausea	6 (3.6)	6 (6.1)	0 (0.0)	0 (0.0)
Vomiting	4 (2.4)	4 (4.1)	0 (0.0)	0 (0.0)
Hypercalcemia	21 (12.6)	16 (16.3)	5 (7.2)	0 (0.0)

Mild hypercalcemia may be asymptomatic or manifest itself as constipation, anorexia, nausea, and vomiting. More severe hypercalcemia is associated with confusion, delirium, stupor, and coma. Decreasing dialysate calcium concentration could reduce the incidence and severity of PhosLo[®]-induced hypercalcemia. Isolated cases pruritus have been reported, which may represent allergic reactions.

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or to establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval of calcium acetate: dizziness, edema, and weakness.

6. Under **DRUG INTERACTIONS**, the section was changed from:

PhosLo may decrease the bioavailability of tetracyclines.

To:

The drug interaction of PhosLo[®] is characterized by the potential of calcium to bind to drugs with anionic functions (e.g., carboxyl, and hydroxyl groups). PhosLo[®] may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between calcium acetate or PhosLo[®] and most concomitant drugs. When administering an oral medication with PhosLo[®] where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy,

administer the drug one hour before or three hours after PhosLo[®] or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials with all forms of calcium acetate.

7.1 Ciprofloxacin

In a study of 15 healthy subjects, a co-administered single dose of 4 calcium acetate tablets, approximately 2.7g, decreased the bioavailability of ciprofloxacin by approximately 50%.

7. Under **USE IN SPECIFIC POPULATIONS/Pregnancy**, the section was changed from:

Teratogenic Effects: Category C. Animal reproduction studies have not been conducted with PhosLo. It is not known whether PhosLo can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PhosLo should be given to a pregnant woman only if clearly needed.

To:

Pregnancy Category C

PhosLo[®] contains calcium acetate. Animal reproduction studies have not been conducted with PhosLo[®], and there are no adequate and well controlled studies of PhosLo[®] 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. PhosLo[®] treatment, as recommended, is not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

8. Under **USE IN SPECIFIC POPULATIONS/Labor and Delivery**, the following information was added:

The effects of PhosLo[®] on labor and delivery are unknown.

9. Under **USE IN SPECIFIC POPULATIONS/Nursing Mothers**, the following information was added:

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

10. Under **USE IN SPECIFIC POPULATIONS/Geriatric Use**, the section was changed from:

Of the total number of subjects in clinical studies of PhosLo (n=91), 25 percent were 65 and over, while 7 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

To:

Clinical studies of calcium acetate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

11. Under **OVERDOSAGE**, the words “may result in” have been added to the first sentence in the first paragraph and a cross reference has been added. The section now reads:

Administration of PhosLo[®] in excess of the appropriate daily dosage may result in hypercalcemia [*see Warnings and Precautions (5.1)*].

12. Under **DESCRIPTION**, the following information has been added as the first sentence of the first paragraph:

PhosLo[®] acts as a phosphate binder. Its chemical name is calcium acetate. Its molecular formula is C₄H₆CaO₄, and its molecular weight is 158.17. Its structural formula is:

13. Under **CLINICAL PHARMACOLOGY**, the section was changed from:

Patients with advanced renal insufficiency (creatinine clearance less than 30 ml/min) exhibit phosphate retention and some degree of hyperphosphatemia. The retention of phosphate plays a pivotal role in causing secondary hyperparathyroidism associated with osteodystrophy, and soft-tissue calcification. The mechanism by which phosphate retention leads to hyperparathyroidism is not clearly delineated. Therapeutic efforts directed toward the control of hyperphosphatemia include reduction in the dietary intake of phosphate, inhibition of absorption of phosphate in the intestine with phosphate binders, and removal of phosphate from the body by more efficient methods of dialysis. The rate of removal of phosphate by dietary manipulation or by dialysis is insufficient. Dialysis patients absorb 40% to 80% of dietary phosphorus. Therefore, the fraction of dietary phosphate absorbed from the diet needs to be reduced by using phosphate binders in most renal failure patients on maintenance dialysis. Calcium

acetate (PhosLo) when taken with meals, combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Maintenance of serum phosphorus below 6.0 mg/dl is generally considered as a clinically acceptable outcome of treatment with phosphate binders. PhosLo is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine. Orally administered calcium acetate from pharmaceutical dosage forms has been demonstrated to be systemically absorbed up to approximately 40% under fasting conditions and up to approximately 30% under nonfasting conditions. This range represents data from both healthy subjects and renal dialysis patients under various conditions.

To:

Patients with ESRD retain phosphorus and can develop hyperphosphatemia. High serum phosphorus can precipitate serum calcium resulting in ectopic calcification. Hyperphosphatemia also plays a role in the development of secondary hyperparathyroidism in patients with ESRD.

12.1 Mechanism of Action

Calcium acetate (PhosLo®), when taken with meals, combines with dietary phosphate to form an insoluble calcium phosphate complex, which is excreted in the feces, resulting in decreased serum phosphorus concentration.

12.2 Pharmacodynamics

Orally administered calcium acetate from pharmaceutical dosage forms is systemically absorbed up to approximately 40% under fasting conditions and up to approximately 30% under non-fasting conditions. This range represents data from both healthy subjects and renal dialysis patients under various conditions

14. Under **NON CLINICAL TOXICOLOGY**, the section was changed from:

Long term animal studies have not been performed to evaluate the carcinogenic potential, mutagenicity, or effect on fertility of PhosLo.

To:

Carcinogenesis, Mutagenesis, Impairment and Fertility

No carcinogenicity, mutagenicity, or fertility studies have been conducted with calcium acetate.

15. Under **CLINICAL STUDIES**, the following information was added:

Effectiveness of calcium acetate in decreasing serum phosphorus has been demonstrated in two studies of the calcium acetate solid oral dosage form.

Ninety-one patients with end-stage renal disease who were undergoing hemodialysis and were hyperphosphatemic (serum phosphorus >5.5 mg/dL)

following a 1-week phosphate binder washout period contributed efficacy data to an open-label, non-randomized study.

The patients received calcium acetate 667 mg tablets at each meal for a period of 12 weeks. The initial starting dose was 2 tablets per meal for 3 meals a day, and the dose was adjusted as necessary to control serum phosphorus levels. The average final dose after 12 weeks of treatment was 3.4 tablets per meal. Although there was a decrease in serum phosphorus, in the absence of a control group the true magnitude of effect is uncertain.

The data presented in Table 2 demonstrate the efficacy of calcium acetate in the treatment of hyperphosphatemia in end-stage renal disease patients. The effects on serum calcium levels are also presented.

Table 2: Average Serum Phosphorous and Calcium Levels at Pre-Study, Interim, and Study Completion Time points

Parameter	Pre-Study	Week 4 ^b	Week 8	Week 12	p-value ^c
Phosphorus (mg/dL) ^a	7.4 ± 0.17	5.9 ± 0.16	5.6 ± 0.17	5.2 ± 0.17	≤0.01
Calcium (mg/dL) ^a	8.9 ± 0.09	9.5 ± 0.10	9.7 ± 0.10	9.7 ± 0.10	≤0.01

^a Values expressed as mean ± SE.

^b Ninety-one patients completed at least 6 weeks of the study.

^c ANOVA of difference in values at pre-study and study completion.

There was a 30% decrease in serum phosphorus levels during the 12 week study period ($p < 0.01$). Two-thirds of the decline occurred in the first month of the study. Serum calcium increased 9% during the study mostly in the first month of the study.

Treatment with the phosphate binder was discontinued for patients from the open-label study, and those patients whose serum phosphorus exceeded 5.5 mg/dL were eligible for entry into a double-blind, placebo-controlled, cross-over study. Patients were randomized to receive calcium acetate or placebo, and each continued to receive the same number of tablets as had been individually established during the previous study. Following 2 weeks of treatment, patients switched to the alternative therapy for an additional 2 weeks.

The phosphate binding effect of calcium acetate is shown in the Table 3.

Table 3: Serum Phosphorous and Calcium Levels at Study Initiation and After Completion of Each Treatment Arm

Parameter	Pre-Study	Post-Treatment		p-value ^b
		Calcium Acetate	Placebo	
Phosphorus (mg/dL) ^a	7.3 ± 0.18	5.9 ± 0.24	7.8 ± 0.22	<0.01
Calcium (mg/dL) ^a	8.9 ± 0.11	9.5 ± 0.13	8.8 ± 0.12	<0.01

^a Values expressed as mean ± SEM

^b ANOVA of calcium acetate vs. placebo after 2 weeks of treatment.

Overall, 2 weeks of treatment with calcium acetate statistically significantly ($p < 0.01$) decreased serum phosphorus by a mean of 19% and increased serum calcium by a statistically significant ($p < 0.01$) but clinically unimportant mean of 7%.

16. Under **PATIENT COUNSELING INFORMATION**, the section was changed from:

The patient should be informed about compliance with dosage instructions, adherence to instructions about diet and avoidance of the use of nonprescription antacids. Patients should be informed about the symptoms of hypercalcemia [(see *Adverse Reactions (6.1)*].

To:

Inform patients to take PhosLo[®] with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform the patients about the symptoms of hypercalcemia [(see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].

Advise patients who are taking an oral medication where reduction in the bioavailability of that medication would have clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after PhosLo[®].

17. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Michael Moneleone, MS
Regulatory Project Manager
(301) 796-1952

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
Agreed-upon Labeling

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

/s/

NORMAN L STOCKBRIDGE
03/29/2011