HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PHOSLYRA® safely and effectively. See full prescribing information for PHOSLYRA.

PHOSLYRA (calcium acetate oral solution)

Initial U.S. Approval: 1990

----------INDICATIONS AND USAGE----------

- PHOSLYRA is a phosphate binder indicated for the reduction of serum phosphorus in patients with end stage renal disease. (1)

----------DOSAGE AND ADMINISTRATION----------

- Starting dose is 10 mL with each meal. (2)
- Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15 to 20 mL with each meal. (2)

---------DOSAGE FORMS AND STRENGTHS----------

- Oral Solution: 667 mg calcium acetate per 5 mL. (3)

----------CONTRAINDICATIONS----------

- Hypercalcemia. (4)

----------WARNINGS AND PRECAUTIONS----------

- Treat mild hypercalcemia by reducing or interrupting PHOSLYRA and Vitamin D. Severe hypercalcemia may require hemodialysis and discontinuation of PHOSLYRA. (5.1)
- May cause diarrhea with nutritional supplements that contain maltitol (5.2)

----------ADVERSE REACTIONS----------

- The most common (>10%) adverse reactions are hypercalcemia, nausea, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Medical Care North America at 1-800-323-5188 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- PHOSLYRA may decrease the bioavailability of tetracyclines fluoroquinolones or levothyroxine. (7)
- When clinically significant drug interactions are expected, separate dosing from PHOSLYRA, or consider monitoring blood levels of the drug. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Management of elevated serum phosphorus levels usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis, and inhibition of intestinal phosphate absorption with phosphate binders.

2 DOSAGE AND ADMINISTRATION

The recommended initial dose of PHOSLYRA for the adult dialysis patient is 10 mL with each meal. Increase the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

3 DOSAGE FORMS AND STRENGTHS

Oral Solution: 667 mg calcium acetate per 5 mL.

4 CONTRAINDICATIONS

Patients with hypercalcemia.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia

Patients with end stage renal disease may develop hypercalcemia when treated with calcium, including calcium acetate (PHOSLYRA). Avoid the concurrent use of calcium supplements, including calcium-based nonprescription antacids, with PHOSLYRA.

An overdose of PHOSLYRA 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 PHOSLYRA 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 PHOSLYRA 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 PHOSLYRA 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 PHOSLYRA 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 a solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment.

Maintain the serum calcium-phosphorus (Ca × P) product below 55 mg^2/dL^2.

5.2 Concomitant Use with Medications

Hypercalcemia may aggravate digitalis toxicity.

PHOSLYRA contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.

6 ADVERSE REACTIONS

No clinical trials have been performed with PHOSLYRA in the intended population. Because the dose and active ingredients of PHOSLYRA are equivalent to that of the calcium acetate gelcaps or tablets, the scope of the adverse reactions is anticipated to be similar.

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 clinical practice.

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

The solid dose formulation of calcium acetate was studied in a 3-month, open-label, non-randomized study of 98 enrolled ESRD hemodialysis patients and 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

	Total adverse reactions reported for calcium acetate n=167	**3-mo, open-label study of calcium acetate n=98**	**Double-blind, placebo-controlled, cross-over study of calcium acetate n=69**	
			Calcium acetate	**Placebo**
Preferred Term	n (%)	n (%)	n (%)	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)

Calcium acetate oral solution was studied in a randomized, controlled, 3-arm, open label, cross-over, single-dose study comparing calcium acetate oral solution to a solid formulation in healthy volunteers on a controlled diet. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with the oral solution.

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.

7 DRUG INTERACTIONS

Oral drugs that have to be separated from Phoslyra	
	Dosing Recommendations
Flouroquinolones	Take at least 2 hours before or 6 hours after Phoslyra
Tetracyclines	Take at least 1 hour before Phoslyra
Levothyroxine	Take at least 4 hours before or 4 hours after Phoslyra

Oral medications not listed in the Table

There are no empirical data on avoiding drug interactions between Phoslyra and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

8.2 Labor and Delivery
The effects of PHOSLYRA on labor and delivery are unknown.

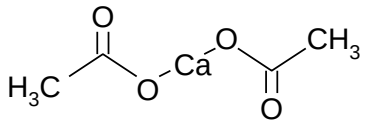
8.3 Nursing Mothers
PHOSLYRA contains calcium acetate and is excreted in human milk. Human milk feeding by a mother receiving Phoslyra is not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.

8.4 Pediatric Use
Safety and effectiveness of PHOSLYRA in pediatric patients have not been established.

8.5 Geriatric Use
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 reported clinical experience has not identified differences in responses between the 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.

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

11 DESCRIPTION
PHOSLYRA acts as a phosphate binder. Its chemical name is calcium acetate. Its molecular formula is $C_4H_6CaO_4$, and its molecular weight is 158.17. Its structural formula is:



PHOSLYRA for oral administration is provided as pale to light greenish-yellow clear liquid. Each 5 mL of PHOSLYRA contains 667 mg calcium acetate, USP equal to 169 mg (8.45 mEq) calcium. PHOSLYRA also contains the following inactive ingredients: maltitol NF, glycerin USP, Magnasweet 110, propylene glycol USP, povidone K25 USP, sucralose NF, methylparaben NF, artificial black cherry flavor, menthol flavor, purified water USP.

12 CLINICAL PHARMACOLOGY
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, 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 concentrations.

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.

A randomized, 3-arm, open-label, cross-over study in healthy volunteers evaluated the bioavailability of PHOSLYRA compared to calcium acetate gelcaps. Each subject received ~1000 mg elemental calcium from each dose of the following study medications: 30 mL PHOSLYRA (test), 6 calcium acetate gelcaps (reference), or 5 calcium citrate caplets (positive control) in three periods. The study medications were administered three times per day with meals from Day 0 through Day 2 and one morning dose on Day 3 of each period.

Treatment (baseline-subtracted) related changes (AUC and C_{max}) in serum calcium and phosphorus assessed over the 6 hours following dosing were similar for PHOSLYRA and calcium acetate gelcaps. Urinary excretion of calcium and phosphorus were not significantly increased with PHOSLYRA compared to calcium acetate gelcaps.

12.3 Pharmcokinetics

Drug Interactions

In vivo

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

Effectiveness of calcium acetate in decreasing serum phosphorus has been demonstrated in two studies of the solid 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 Phosphorus 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 Table 3.

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

		Post-Treatment		
Parameter	Pre-Study	*Calcium Acetate*	*Placebo*	p-value[b]
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 HOW SUPPLIED/STORAGE AND HANDLING

PHOSLYRA for oral administration is a clear solution containing 667 mg calcium acetate per 5 mL. PHOSLYRA is supplied in amber-colored, multiple-dose bottles, packaged with a marked dosing cup in the following size:
473 mL (16 fl. oz) bottle.....(NDC 49230-643-31)

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

The shelf life is 24 months.

17 PATIENT COUNSELING INFORMATION

Inform patients to take PHOSLYRA with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform 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 a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after PHOSLYRA.

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Manufactured by:
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101087.C 10/2015

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