HIGHLIGHTS OF PRESCRIBING INFORMATION

Calcium Acetate Capsules

These highlights do not include all the information needed to use Calcium Acetate Capsules safely and effectively. See full prescribing information for Calcium Acetate Capsules.

CALCIUM Acetate Capsules for ORAL use.

Initial U.S. Approval: 1990

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

- Calcium Acetate Capsule 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 2 capsules with each meal. (2)
- Titrate the dose every 2 to 3 weeks until acceptable serum phosphorus level is reached. Most patients require 3 to 4 capsules with each meal. (2)

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

- Capsule: 667 mg calcium acetate. (3)

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

- Hypercalcemia. (4)

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

- Treat mild hypercalcemia by reducing or interrupting calcium acetate and Vitamin D. Severe hypercalcemia may require hemodialysis and discontinuation of calcium acetate. (5.1)
- Hypercalcemia may aggravate digitalis toxicity. (5.2)

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

- The most common (>10%) adverse reactions are hypercalcemia, nausea, and vomiting. (6.1).
- In clinical studies, patients have occasionally experienced nausea during calcium acetate therapy. (6).

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Calcium acetate may decrease the bioavailability of tetracyclines or fluoroquinolones. (7)
- When clinically significant drug interactions are expected, administer the drug at least one hour before or at least three hours after calcium acetate, or consider monitoring blood levels of the drug. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2013

FULL PRESCRIBING INFORMATION:

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

The recommended initial dose of calcium acetate capsule for the adult dialysis patient is 2 capsules with each meal. Increase the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Most patients require 3 to 4 capsules with each meal.

3 DOSAGE FORMS AND STRENGTHS

Capsule: 667 mg calcium acetate per capsule.

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. Avoid the use of calcium supplements, including calcium-based nonprescription antacids, concurrently with calcium acetate.

An overdose of calcium acetate 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 calcium acetate 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 calcium acetate 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 calcium acetate 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 calcium acetate 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 x P) product below 55 mg^2/dL^2.

5.2 Concomitant Use with Medications

Hypercalcemia may aggravate digitalis toxicity.

6 ADVERSE REACTIONS

Hypercalcemia is discussed elsewhere [see **WARNINGS AND PRECAUTIONS (5.1)**].

6.1 Clinical Trials 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.

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

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 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 calcium acetate -induced hypercalcemia. Isolated cases of 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.

7 DRUG INTERACTIONS

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

There are no empirical data on avoiding drug interactions between calcium acetate or calcium acetate capsules and most concomitant drugs. When administering an oral medication with calcium acetate 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 calcium acetate capsules 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 2.7 g, decreased the bioavailability of ciprofloxacin by approximately 50%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Calcium acetate capsules contain calcium acetate. Animal reproduction studies have not been conducted with calcium acetate, and there are no adequate and well controlled studies of calcium acetate 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. Calcium acetate 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 calcium acetate on labor and delivery are unknown.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

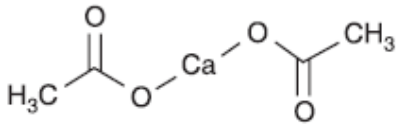
Clinical studies of calcium acetate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection 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 calcium acetate in excess of the appropriate daily dosage may result in hypercalcemia [see **WARNINGS AND PRECAUTIONS (5.1)**].

11 DESCRIPTION

Calcium acetate 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:



Each capsule with a blue cap and white body is imprinted with “LU” in white ink on the cap and “G41” in blue ink on the body containing white to off-white granular powder. Each capsule contains 667 mg calcium acetate, USP (anhydrous; $Ca(CH_3COO)_2$; MW=158.17 grams) equal to 169 mg (8.45 mEq) calcium, magnesium stearate and polyethylene glycol 8000. The gelatin cap and body have the following inactive ingredients: D and C red 28, FD & C blue #2 aluminum lake, FD & C blue 1, gelatin, potassium hydroxide, propylene glycol, shellac and titanium dioxide.

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 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.

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 calcium acetate 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 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 Phosphorus 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 ± SE.

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

Overall, 2 weeks of treatment with calcium acetate statistically significantally ($p<0.01$) 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

Calcium Acetate Capsules are **s**ize "00" capsules with blue cap and white body, imprinted with "LU" in white ink on the cap and "G41" in blue ink on the body containing white to off-white granular powder for oral administration containing 667 mg calcium acetate (anhydrous $Ca(CH_3COO)_2$; MW=158.17 grams) equal to 169 mg (8.45 mEq) calcium.

Bottle of 200 capsules NDC 68180-134-15

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

17 PATIENT COUNSELING INFORMATION

Inform patients to take calcium acetate capsules 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 and efficacy to take the drug one hour before or three hours after calcium acetate capsules.

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