CALCIUM ACETATE- calcium acetate capsule
Amneal Pharmaceuticals LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CALCIUM ACETATE capsules: 667 mg, for oral use
Initial U.S. Approval: 1990

INDICATIONS AND USAGE

- Calcium acetate capsules are 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 capsule. (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 Amneal Pharmaceuticals at 1-877-835-5472 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: 9/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

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

2 DOSAGE & ADMINISTRATION

The recommended initial dose of calcium acetate capsules 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 & STRENGTHS

- Capsule: 667 mg calcium acetate, USP 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 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 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 advers 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)
Vomiting	4 (2.4)	4 (4.1)	0 (0)	0 (0)
Hypercalcemia	21 (12.6)	16 (16.3)	5 (7.2)	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 capsules 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 capsules contain 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

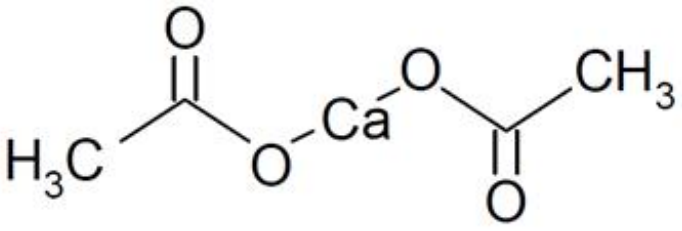
Clinical studies of calcium acetate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection 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, USP acts as a phosphate binder. Its chemical name is calcium acetate, USP. Its molecular formula is $C_4H_6CaO_4$, and its molecular weight is 158.17. Its structural formula is:



Each capsule has a light-blue cap imprinted with “AMNEAL” and white body imprinted with “590” with black ink. 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. Each capsule also contains the following inactive ingredients: FD&C Blue #1, FD&C Red #3, gelatin, magnesium stearate, polyethylene glycol and titanium dioxide. In addition to the inactive ingredients listed above, each capsule contains Opacode (Black) monogramming ink. Opacode (Black) contains D&C Yellow #10, FD&C Blue #2, FD&C Red #40, iron oxide black and shellac. Opacode (Black) may also contain ethanol, methanol, n-butyl alcohol and propylene glycol.

Calcium acetate capsules, USP are administered orally for the control of hyperphosphatemia in end-stage renal failure.

USP dissolution test pending.

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 nonfasting 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 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 HOW SUPPLIED/STORAGE AND HANDLING

Calcium acetate capsules USP, **667 mg** are available as hard gelatin capsules with white opaque body imprinted with “590” and light-blue opaque cap imprinted with “AMNEAL” with black ink. 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.

They are supplied as follows:

Bottles of 100:	NDC 65162-590-10
Bottles of 200:	NDC 65162-590-20
Bottles of 500:	NDC 65162-590-50

STORAGE: Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

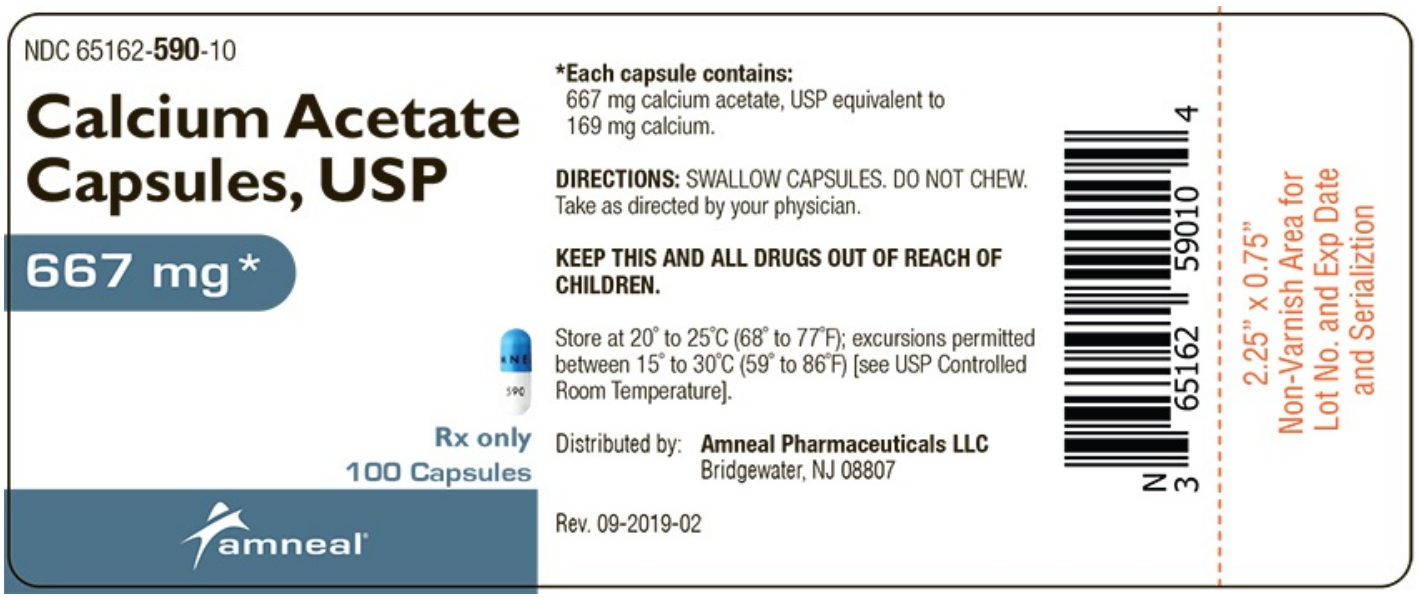
Inform patients to take calcium acetate with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform the patients about the symptoms of hypercalcemia *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*.

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 calcium acetate.

Distributed By:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 09-2019-02

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



CALCIUM ACETATE

calcium acetate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65162-590
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CALCIUM ACETATE (UNII: Y882YXF34X) (CALCIUM CATION - UNII:2M83C4R6ZB)	CALCIUM ACETATE	667 mg

Inactive Ingredients	
Ingredient Name	**Strength**
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
ALCOHOL (UNII: 3K9958V90M)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
METHYL ALCOHOL (UNII: Y4S76JWI15)	

BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	

Product Characteristics

Color	white (body) , blue (cap)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	AMNEAL;590
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65162-590-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/08/2014	
2	NDC:65162-590-20	200 in 1 BOTTLE; Type 0: Not a Combination Product	10/08/2014	
3	NDC:65162-590-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	10/08/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201658	10/08/2014	

Labeler - Amneal Pharmaceuticals LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals of New York, LLC		123797875	analysis(65162-590) , label(65162-590) , manufacture(65162-590) , pack(65162-590)

Revised: 9/2019 Amneal Pharmaceuticals LLC