

# LANTHANUM CARBONATE- lanthanum carbonate tablet, chewable

## Prasco Laboratories

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LANTHANUM CARBONATE chewable tablets, for oral use

Initial U.S. Approval: 2004

### RECENT MAJOR CHANGES

Warnings and Precautions (5.1)

11/2018

### INDICATIONS AND USAGE

- LANTHANUM CARBONATE is a phosphate binder indicated to reduce serum phosphate in patients with end stage renal disease (ESRD). (1)

### DOSAGE AND ADMINISTRATION

- The recommended initial total daily dose of LANTHANUM CARBONATE is 1500 mg in divided doses. Titrate every 2-3 weeks based on serum phosphate level. (2)
- Take LANTHANUM CARBONATE with or immediately after meals. (2)
- Chew or crush tablet completely before swallowing. (2)

### DOSAGE FORMS AND STRENGTHS

- LANTHANUM CARBONATE Chewable Tablets: 500 mg, 750 mg, and 1000 mg. (3)

### CONTRAINDICATIONS

- Bowel obstruction, ileus, and fecal impaction. (4)

### WARNINGS AND PRECAUTIONS

- Serious cases of gastrointestinal obstruction, ileus, subileus, gastrointestinal perforation and fecal impaction. Risks include altered gastrointestinal anatomy, hypomotility disorders, and concomitant medications. Advise patients to chew or crush the tablet completely. (5.1)
- LANTHANUM CARBONATE has radio-opaque properties and therefore may give the appearance typical of an imaging agent during abdominal X-ray procedures. (5.2)

### ADVERSE REACTIONS

- In controlled trials, the most common adverse reactions that were more frequent ( $\geq 5\%$  difference vs. placebo) in LANTHANUM CARBONATE were nausea, vomiting and abdominal pain. (6.1)
- The following adverse reactions have been identified during post-approval use of LANTHANUM CARBONATE: constipation, dyspepsia, allergic skin reactions, and tooth injury while chewing the tablet. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### DRUG INTERACTIONS

- There is a potential for LANTHANUM CARBONATE to interact with compounds that bind to cationic antacids (i.e., aluminum-, magnesium-, or calcium-based). Therefore, do not take such compounds within 2 hours of dosing with LANTHANUM CARBONATE. (7.1)
- Oral quinolone antibiotics must be taken at least 1 hour before or 4 hours after LANTHANUM CARBONATE. (7.2)
- Do not take thyroid hormone replacement therapy within 2 hours of dosing with LANTHANUM CARBONATE. Monitoring of TSH levels is recommended in patients receiving both medicinal agents. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2018

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

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

LANTHANUM CARBONATE is a phosphate binder indicated to reduce serum phosphate in patients with end stage renal disease (ESRD).

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

## 2 DOSAGE AND ADMINISTRATION

Divide the total daily dose of LANTHANUM CARBONATE and take with or immediately after meals. The recommended initial total daily dose of LANTHANUM CARBONATE is 1500 mg. Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached. Monitor serum phosphate levels as needed during dose titration and on a regular basis thereafter.

In clinical studies of ESRD patients, LANTHANUM CARBONATE doses up to 4500 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750 mg/day.

**Chew or crush LANTHANUM CARBONATE completely before swallowing. Do not swallow intact LANTHANUM CARBONATE Chewable Tablets.**

Consider using the oral powder formulation in patients with poor dentition or who have difficulty chewing tablets.

## 3 DOSAGE FORMS AND STRENGTHS

LANTHANUM CARBONATE Chewable Tablets: 500 mg, 750 mg, and 1000 mg.

## 4 CONTRAINDICATIONS

Contraindicated in bowel obstruction, including ileus and fecal impaction.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Gastrointestinal Adverse Effects

Serious cases of gastrointestinal obstruction, ileus, subileus, gastrointestinal perforation and fecal impaction have been reported in patients taking lanthanum, some requiring surgery or hospitalization. Consider discontinuing LANTHANUM CARBONATE in patients without another explanation for severe gastrointestinal symptoms.

Risk factors for gastrointestinal obstruction and gastrointestinal perforation identified from post-marketing reports in patients taking LANTHANUM CARBONATE Chewable Tablets include altered gastrointestinal anatomy (e.g., diverticular disease, peritonitis, history of gastrointestinal surgery, gastrointestinal cancer, gastrointestinal ulceration), hypomotility disorders (e.g., constipation, ileus, subileus, diabetic gastroparesis), and the use of medications known to potentiate these effects. Some cases were reported in patients with no history of gastrointestinal disease.

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in LANTHANUM CARBONATE clinical studies [see *Contraindications (4)*].

Advise patients who are prescribed LANTHANUM CARBONATE Chewable Tablets to chew the tablet completely and not to swallow them whole. Serious gastrointestinal complications have been reported in association with unchewed or incompletely chewed tablets [see *Adverse Reactions (6.2)*].

### 5.2 Diagnostic Tests

LANTHANUM CARBONATE has radio-opaque properties and therefore may give the appearance typical of an imaging agent during abdominal X-ray procedures.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Gastrointestinal Adverse Effects [see *Warnings and Precautions (5.1)*]

Overall, the safety profile of LANTHANUM CARBONATE has been studied in over 5200 subjects in completed clinical trials. The most common adverse reactions for LANTHANUM CARBONATE were gastrointestinal events, such as nausea, vomiting, and abdominal pain and they generally abated over time with continued dosing.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 double-blind, placebo-controlled studies where a total of 180 and 95 ESRD patients were randomized to LANTHANUM CARBONATE chewable tablet and placebo, respectively, for 4-6 weeks of treatment, the most common reactions that were more frequent ( $\geq 5\%$  difference) in the LANTHANUM CARBONATE group were nausea, vomiting, and abdominal pain (Table 1).

**Table 1. Adverse Reactions\* That Were More Common on LANTHANUM CARBONATE in Placebo-Controlled, Double-Blind Studies With Treatment Periods of 4-6 Weeks**

	<b>LANTHANUM CARBONATE % (N=180)</b>	<b>Placebo % (N=95)</b>
Nausea	11	5
Vomiting	9	4
Abdominal pain	5	0

\* expressed as the event rate for each term

In an open-label long-term 2 year extension study in 93 patients who had transitioned from other studies, resulting in a total of up to 6 years treatment, mean baseline values and changes in transaminases were similar to those observed in the earlier comparative studies, with little change during treatment.

The safety of LANTHANUM CARBONATE was studied in two long-term, open-labeled clinical trials, which included 1215 patients treated with LANTHANUM CARBONATE and 944 with alternative therapy. Fourteen percent (14%) of LANTHANUM CARBONATE treated patients discontinued treatment due to adverse events. Gastrointestinal adverse reactions, such as nausea, diarrhea and vomiting were the most common types of event leading to discontinuation.

In pooled active comparator controlled clinical trials, hypocalcemia was noted with an incidence of approximately 5% in both lanthanum and active comparator groups. A nonclinical study and a phase 1 study have shown reduced absorption of calcium in the intestine with lanthanum carbonate treatment.

In a crossover study in 72 healthy individuals comparing LANTHANUM CARBONATE chewable tablets to LANTHANUM CARBONATE oral powder, gastrointestinal adverse reactions such as nausea, diarrhea and vomiting were more common for the oral powder formulation (18%) than for the chewable tablets (7%).

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LANTHANUM CARBONATE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: constipation, intestinal perforation, intestinal obstruction, ileus, subileus, dyspepsia, allergic skin reactions, hypophosphatemia, and tooth injury while chewing the tablet.

## 7 DRUG INTERACTIONS

Lanthanum in LANTHANUM CARBONATE has the potential to bind to drugs with anionic (e.g., carboxyl, carbonyl and hydroxyl) groups. LANTHANUM CARBONATE may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between LANTHANUM CARBONATE 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.

### 7.1 Drugs Binding to Antacids

There is a potential for LANTHANUM CARBONATE to interact with compounds which bind to cationic antacids (i.e., aluminum-, magnesium-, or calcium-based). Therefore, do not administer such compounds within 2 hours of dosing with LANTHANUM CARBONATE. Examples of relevant classes of compounds where antacids have been demonstrated to reduce bioavailability include antibiotics (such as quinolones, ampicillin and tetracyclines), thyroid hormones, ACE-inhibitors, statin lipid regulators and anti-malarials.

### 7.2 Quinolone Antibiotics

Co-administration of LANTHANUM CARBONATE with quinolone antibiotics may reduce the extent of their absorption. The bioavailability of oral ciprofloxacin was decreased by approximately 50% when taken with LANTHANUM CARBONATE in a single dose study in healthy volunteers. Administer oral quinolone antibiotics at least 1 hour before or 4 hours after LANTHANUM CARBONATE. When oral quinolones are given for short courses, consider eliminating the doses of LANTHANUM CARBONATE that would be normally scheduled near the time of quinolone intake to improve quinolone absorption [see *Clinical Pharmacology (12.3)*].

### 7.3 Levothyroxine

The bioavailability of levothyroxine was decreased by approximately 40% when taken together with LANTHANUM CARBONATE. Administer thyroid hormone replacement therapy at least 2 hours before or 2 hours after dosing with LANTHANUM CARBONATE and monitor thyroid stimulating hormone (TSH) levels [see *Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. The effect of LANTHANUM CARBONATE on the absorption of vitamins and other nutrients has not been studied in pregnant women. LANTHANUM CARBONATE is not recommended for use during pregnancy.

Studies in pregnant rabbits showed that oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the maximum recommended daily human dose (MRHD) of 5725 mg, on a mg/m<sup>2</sup> basis, assuming a 60 kg patient) was associated with increased post-implantation loss, reduced fetal weights, and delayed fetal ossification [see *Nonclinical Toxicology (13.3)*].

### 8.2 Labor and Delivery

No LANTHANUM CARBONATE treatment-related effects on labor and delivery were seen in animal studies. The effect of LANTHANUM CARBONATE on labor and delivery in humans is unknown.

### **8.3 Nursing Mothers**

It is not known whether lanthanum carbonate is excreted in human milk. As many drugs are excreted in human milk, consider the possibility of infant exposure when LANTHANUM CARBONATE is administered to a nursing woman.

### **8.4 Pediatric Use**

The safety and efficacy of LANTHANUM CARBONATE in pediatric patients have not been established. While growth abnormalities were not identified in long-term animal studies, lanthanum was deposited into developing bone including growth plate. The consequences of such deposition in developing bone in pediatric patients are unknown. Therefore, the use of LANTHANUM CARBONATE in this population is not recommended.

### **8.5 Geriatric Use**

Of the total number of patients in clinical studies of LANTHANUM CARBONATE, 32% (538) were  $\geq 65$ , while 9.3% (159) were  $\geq 75$ . No overall differences in safety or effectiveness were observed between patients  $\geq 65$  years of age and younger patients.

## **10 OVERDOSAGE**

The symptoms associated with overdose are adverse reactions such as headache, nausea and vomiting. In clinical trials in healthy adults, GI symptoms were reported with daily doses up to 6000 mg/day of lanthanum carbonate administered with food. Given the topical activity of lanthanum in the gut, and the excretion in feces of the majority of the dose, supportive therapy is recommended for overdosage. Lanthanum carbonate was not acutely toxic in animals by the oral route. No deaths and no adverse effects occurred in mice, rats or dogs after single oral doses of 2000 mg/kg (1.7, 3.4, and 11.3 times the MRHD, respectively, on a mg/m<sup>2</sup> basis).

## **11 DESCRIPTION**

LANTHANUM CARBONATE contains lanthanum carbonate with molecular formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  (on average  $x=4-5$  moles of water) and molecular weight 457.8 (anhydrous mass). Lanthanum carbonate is described as white to almost white powder. Lanthanum carbonate is practically insoluble in water and is insoluble in organic solvents; it dissolves in dilute mineral acids with effervescence.

Each LANTHANUM CARBONATE white to off-white, chewable tablet contains lanthanum carbonate hydrate equivalent to 500, 750, or 1000 mg of elemental lanthanum and the following inactive ingredients: colloidal silicon dioxide NF, dextrates (hydrated) NF, magnesium stearate NF.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

LANTHANUM CARBONATE is a phosphate binder that reduces absorption of phosphate by forming insoluble lanthanum phosphate complexes that pass through the gastrointestinal (GI) tract unabsorbed. Both serum phosphate and calcium phosphate product are reduced as a consequence of the reduced dietary phosphate absorption.

### **12.2 Pharmacodynamics**

*In vitro* studies have shown that lanthanum binds phosphate in the physiologically relevant pH range of 3

to 7. In simulated gastric fluid, lanthanum binds approximately 97% of the available phosphate at pH 3-5 and 67% at pH 7, when lanthanum is present in a two-fold molar excess to phosphate. Bile acids have not been shown to affect the phosphate binding affinity of lanthanum. In order to bind dietary phosphate, LANTHANUM CARBONATE must be administered with or immediately after meals.

In five Phase I pharmacodynamic studies comparing the reduction from baseline of urinary phosphorus excretion in healthy volunteers (N=143 taking lanthanum carbonate), it was shown that the mean intestinal phosphate binding capacity of lanthanum ranged from 235 to 468 mg phosphorus/day when lanthanum was administered at a dose of 3 g per day with food. By comparison, in one study with an untreated control group (n=10) and another study with a placebo group (n=3), the corresponding mean changes from baseline were 3 mg phosphorus/day and 87 mg phosphorus/day, respectively.

In healthy subjects LANTHANUM CARBONATE Oral Powder was found to be similar to LANTHANUM CARBONATE Chewable Tablets, based on urinary phosphate excretion.

### 12.3 Pharmacokinetics

*Absorption and Distribution* - Following single or multiple dose oral administration of LANTHANUM CARBONATE to healthy subjects, the concentration of lanthanum in plasma was very low (bioavailability <0.002%). Following oral administration in patients, the mean lanthanum  $C_{max}$  was 1.0 ng/mL. During long-term administration (52 weeks) in ESRD patients, the mean lanthanum concentration in plasma was approximately 0.6 ng/mL. There was minimal increase in plasma lanthanum concentrations with increasing doses within the therapeutic dose range. The timing of food intake relative to lanthanum administration (during and 30 minutes after food intake) has a negligible effect on the systemic level of lanthanum.

Systemic exposure to lanthanum was approximately 30% higher following administration of LANTHANUM CARBONATE Oral Powder when compared to LANTHANUM CARBONATE Chewable Tablets. However, systemic exposure to lanthanum from both formulations in this study was within the range seen in previous pharmacokinetic studies of Chewable Tablets in healthy individuals.

*In vitro*, lanthanum is highly bound (>99%) to human plasma proteins, including human serum albumin,  $\alpha$ 1-acid glycoprotein, and transferrin. Binding to erythrocytes *in vivo* is negligible in rats.

In animal studies, lanthanum concentrations in several tissues, particularly gastrointestinal tract, mesenteric lymph nodes, bone and liver, increased over time to levels several orders of magnitude higher than those in plasma. The level of lanthanum in the liver was higher in renally impaired rats due to higher intestinal absorption. Lanthanum was found in the lysosomes and the biliary canal consistent with transcellular transport. Steady state tissue concentrations in bone and liver were achieved in dogs between 4 and 26 weeks. Relatively high levels of lanthanum remained in these tissues for longer than 6 months after cessation of dosing in dogs. There is no evidence from animal studies that lanthanum crosses the blood-brain barrier.

In 105 bone biopsies from patients treated with LANTHANUM CARBONATE for up to 4.5 years, rising levels of lanthanum were noted over time. Estimates of elimination half-life from bone ranged from 2.0 to 3.6 years. Steady state bone concentrations were not reached during the period studied.

*Metabolism and Elimination* - Lanthanum is not metabolized. Lanthanum was cleared from plasma of patients undergoing dialysis with an elimination half-life of 53 hours following discontinuation of therapy.

No information is available regarding the mass balance of lanthanum in humans after oral administration. In rats and dogs, the mean recovery of lanthanum after an oral dose was about 99% and 94%, respectively, and was essentially all from feces. Biliary excretion is the predominant route of elimination for circulating lanthanum in rats. In healthy volunteers administered intravenous lanthanum as the soluble chloride salt (120  $\mu$ g), renal clearance was less than 2% of total plasma clearance.

### *Drug Interactions*

LANTHANUM CARBONATE has a low potential for systemic drug-drug interactions because of the very low bioavailability of lanthanum and because it is not a substrate or inhibitor of major cytochrome P450 enzyme groups involved in drug metabolism (CYP1A2, CYP2C9/10, CYP2C19, CYP2D6 and CYP3A4/5).

LANTHANUM CARBONATE does not alter gastric pH. Therefore, LANTHANUM CARBONATE drug interactions based on altered gastric pH are not expected.

In an *in vitro* investigation, lanthanum did not form insoluble complexes when mixed in simulated gastric fluid with warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril. Clinical studies have shown that LANTHANUM CARBONATE (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of co-administration) administered 30 minutes earlier did not alter the pharmacokinetics of oral warfarin (10 mg), digoxin (0.5 mg), or metoprolol (100 mg). Potential pharmacodynamic interactions between lanthanum and these drugs (e.g., bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies were done with the maximum recommended therapeutic dose of lanthanum carbonate. No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

#### Ciprofloxacin

In a randomized, two-way crossover study in healthy volunteers examining the interaction potential of a single oral dose of ciprofloxacin (750 mg) alone and with lanthanum carbonate (1 g TID), the maximum plasma concentration of ciprofloxacin was reduced by 56% and the area under the ciprofloxacin plasma concentration-time curve was reduced by 54%. The 24-h urinary recovery of ciprofloxacin was reduced 52% by LANTHANUM CARBONATE [see *Drug Interactions* (7.2)].

#### Levothyroxine

In a single-dose crossover study of levothyroxine (1 mg) with or without simultaneous administration of a single dose of LANTHANUM CARBONATE (500 mg) in six euthyroid normal healthy volunteers, the area under the serum T4 concentration-time curve was decreased by 40% [see *Drug Interactions* (7.3)].

#### Fat Soluble Vitamins

LANTHANUM CARBONATE appears not to affect the availability of fat soluble vitamins (A, D, E and K) or other nutrients [see *Clinical Studies* (14.2)].

#### Citrate

Citrate did not increase the absorption of lanthanum.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg of the salt per kg/day [2.5 times the MRHD of 5725 mg, on a mg/m<sup>2</sup> basis, assuming a 60-kg patient] revealed no evidence of carcinogenic potential. In the mouse, oral administration of lanthanum carbonate for up to 99 weeks, at a dose of 1500 mg/kg/day (1.3 times the MRHD) was associated with an increased incidence of glandular stomach adenomas in male mice.

Lanthanum carbonate tested negative for mutagenic activity in an *in vitro* Ames assay using *Salmonella typhimurium* and *Escherichia coli* strains and *in vitro* HGPRT gene mutation and chromosomal aberration assays in Chinese hamster ovary cells. Lanthanum carbonate also tested negative in an oral mouse micronucleus assay at doses up to 2000 mg/kg (1.7 times the MRHD), and in micronucleus and unscheduled DNA synthesis assays in rats given IV lanthanum chloride at doses up to 0.1 mg/kg, a dose that produced plasma lanthanum concentrations >2000 times the peak human plasma concentration.

Lanthanum carbonate, at doses up to 2000 mg/kg/day (3.4 times the MRHD), did not affect fertility or



mating performance of male or female rats.

### 13.3 Developmental Toxicity

In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption, increased post-implantation loss, reduced fetal weights, and delayed fetal ossification. Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

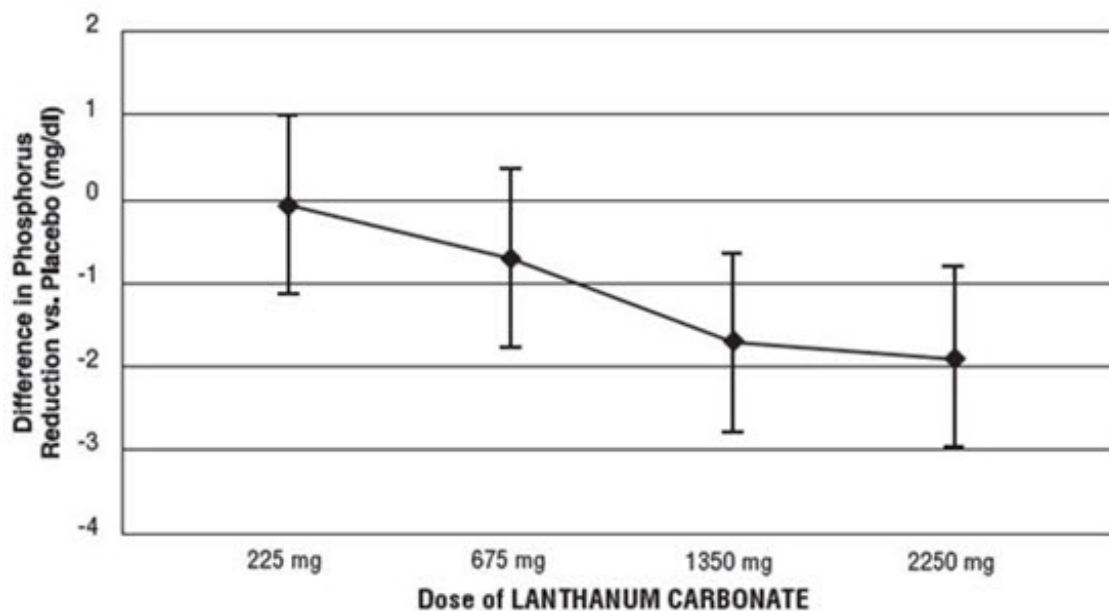
## 14 CLINICAL STUDIES

The effectiveness of LANTHANUM CARBONATE in reducing serum phosphorus in ESRD patients was demonstrated in one short-term, placebo-controlled, double-blind dose-ranging study, two placebo-controlled randomized withdrawal studies and two long-term, active-controlled, open-label studies in both hemodialysis and peritoneal dialysis (PD) patients.

### 14.1 Double-Blind Placebo-Controlled Studies

One hundred and forty-four patients with chronic renal failure undergoing hemodialysis and with elevated phosphate levels were randomized to double-blind treatment at a fixed dose of lanthanum carbonate of 225 mg (n=27), 675 mg (n=29), 1350 mg (n=30) or 2250 mg (n=26) or placebo (n=32) in divided doses with meals. Fifty-five percent of subjects were male, 71% black, 25% white and 4% of other races. The mean age was 56 years and the duration of dialysis ranged from 0.5 to 15.3 years. Steady-state effects were achieved after two weeks. The effect after six weeks of treatment is shown in Figure 1.

**Figure 1. Difference in Phosphate Reduction in the LANTHANUM CARBONATE and Placebo Group in a 6-Week, Dose-Ranging, Double-Blind Study in ESRD Patients (with 95% Confidence Intervals)**



One-hundred and eighty-five patients with end stage renal disease undergoing either hemodialysis (n=146) or peritoneal dialysis (n=39) were enrolled in two placebo-controlled, randomized withdrawal studies. Sixty-four percent of subjects were male, 28% black, 62% white and 10% of other races. The

mean age was 58.4 years and the duration of dialysis ranged from 0.2 to 21.4 years. After titration of lanthanum carbonate to achieve a phosphate level between 4.0 and 5.6 mg/dL in one study (doses up to 2250 mg/day) or  $\leq 5.9$  mg/dL in the second study (doses up to 3000 mg/day) and maintenance through 6 weeks, patients were randomized to lanthanum or placebo. During the placebo-controlled, randomized withdrawal phase (four weeks), the phosphorus concentration rose in the placebo group by 1.7 mg/dL in one study and 1.9 mg/dL in the other study relative to patients who remained on lanthanum carbonate therapy.

#### **14.2 Open-Label Active-Controlled Studies**

Two long-term open-label studies were conducted, involving a total of 2028 patients with ESRD undergoing hemodialysis. Patients were randomized to receive LANTHANUM CARBONATE or alternative phosphate binders for up to six months in one study and two years in the other. The daily LANTHANUM CARBONATE doses, divided and taken with meals, ranged from 375 mg to 3000 mg. Doses were titrated to reduce serum phosphate levels to a target level. The daily doses of the alternative therapy were based on current prescribing information or those commonly utilized. Both treatment groups had similar reductions in serum phosphate of about 1.8 mg/dL. Maintenance of reduction was observed for up to three years in patients treated with LANTHANUM CARBONATE in long-term, open-label extensions.

No effects of LANTHANUM CARBONATE on serum levels of 25-dihydroxy vitamin D<sub>3</sub>, vitamin A, vitamin B<sub>12</sub>, vitamin E and vitamin K were observed in patients who were monitored for 6 months.

Paired bone biopsies (at baseline and at one or two years) in 69 patients randomized to either LANTHANUM CARBONATE or calcium carbonate in one study and 99 patients randomized to either LANTHANUM CARBONATE or alternative therapy in a second study showed no differences in the development of mineralization defects between the groups.

Vital status was known for over 2000 patients, 97% of those participating in the clinical program during and after receiving treatment. The adjusted yearly mortality rate (rate/years of observation) for patients treated with LANTHANUM CARBONATE or alternative therapy was 6.6%.

### **16 HOW SUPPLIED/STORAGE AND HANDLING**

LANTHANUM CARBONATE is supplied as a chewable tablet in three dosage strengths for oral administration: 500 mg tablets, 750 mg tablets, and 1000 mg tablets. Each chewable tablet is white to off-white round, flat with a bevelled edge, and debossed on one side with 'S405' and the dosage strength corresponding to the content of elemental lanthanum.

500 mg Patient Pack (2 bottles of 45 tablets, NDC 66993-422-47, per each patient pack) NDC 66993-422-85.

750 mg Patient Pack (6 bottles of 15 tablets, NDC 66993-423-53, per each patient pack) NDC 66993-423-85.

1000 mg Patient Pack (9 bottles of 10 tablets, NDC 66993-424-75, per each patient pack) NDC 66993-424-85.

Storage - Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

[See USP controlled room temperature].

### **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients to take LANTHANUM CARBONATE with or immediately after meals [*see Dosage and Administration (2)*].

Instruct patients on concomitant medications that should be dosed apart from LANTHANUM CARBONATE [see *Drug Interactions (7)*].

**Instruct patients who are prescribed LANTHANUM CARBONATE Chewable Tablets to chew or crush tablets completely before swallowing.** Emphasize that LANTHANUM CARBONATE Chewable Tablets should not be swallowed intact. Consider crushing LANTHANUM CARBONATE Chewable Tablets completely or prescribing the oral powder formulation for patients with poor dentition or who have difficulty chewing tablets [see *Dosage and Administration (2)*].

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 separate the dosing of LANTHANUM CARBONATE from the dosing of the affected drug by several hours [see *Drug Interactions (7)*].

Advise patients to notify their physician that they are taking LANTHANUM CARBONATE prior to an abdominal X-ray or if they have a history of gastrointestinal disease [see *Warnings and Precautions (5.1, 5.2)*].

LANTHANUM CARBONATE Chewable Tablets manufactured by Patheon Manufacturing Services LLC,  
5900 Martin Luther King Jr. Highway,  
Greenville, NC 27834

Distributed by:  
**Prasco Laboratories**  
Mason, OH 45040

Manufactured for **Shire US Inc.**, 300 Shire Way, Lexington, MA 02421.

This product is covered by US patents 5,968,976, 7,465,465, 8,980,327 and 9,023,397.

## **MEDICATION GUIDE**

### **LANTHANUM CARBONATE**

Read this Medication Guide before you start taking LANTHANUM CARBONATE and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

#### **What is the most important information I should know about LANTHANUM CARBONATE?**

LANTHANUM CARBONATE may cause a bowel blockage, a hole in the bowel, or severe constipation which can be serious, and sometimes lead to surgery or treatment in a hospital.

- You may have a higher risk of bowel blockage, a hole in the bowel or severe constipation if you take LANTHANUM CARBONATE and have:
  - a history of surgery, ulcers or cancer in the stomach or bowel
  - a history of bowel blockage, or problems resulting in a decreased movement of food through your stomach and bowel (e.g. feeling full quickly after eating or constipation)
  - an infection or inflammation of the stomach/bowel (peritonitis)

**Do not swallow LANTHANUM CARBONATE Chewable Tablets whole. Chew tablets completely before swallowing. If you can not chew tablets completely, you may crush the tablets thoroughly before swallowing or discuss the oral powder formulation with your healthcare provider.**

#### **What is LANTHANUM CARBONATE?**

LANTHANUM CARBONATE is a prescription medicine used in people with end stage renal disease (ESRD) to lower the amount of phosphate in the blood.

## **Who should not take LANTHANUM CARBONATE?**

Do not take LANTHANUM CARBONATE if you:

- have blocked bowels
- have severe constipation

LANTHANUM CARBONATE has not been studied in children and adolescents under 18 years of age.

## **What should I tell my healthcare provider before taking LANTHANUM CARBONATE?**

**LANTHANUM CARBONATE may not be right for you. Before starting LANTHANUM CARBONATE, tell your healthcare provider if you:**

- have a history of surgery, ulcers or cancer in the stomach or bowel
- have a history of a bowel blockage, constipation, or problems resulting in a decreased movement of food through your stomach and bowel especially if you also have diabetes
- have ulcerative colitis, Crohn's disease or an infection or inflammation of the stomach/bowel (peritonitis)
- plan to have an X-ray of your stomach (abdomen)
- have any other medical conditions
- are pregnant, plan to become pregnant, or plan to breastfeed. It is not known if LANTHANUM CARBONATE will harm your unborn baby

**Tell your healthcare provider about all of the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- antacids
- antibiotics
- thyroid medicine

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

## **How should I take LANTHANUM CARBONATE?**

- Take LANTHANUM CARBONATE exactly as prescribed by your healthcare provider
- Your healthcare provider will tell you how much LANTHANUM CARBONATE to take
- Your healthcare provider may change your dose if needed
- **Do not swallow tablets whole. Chew tablets completely before swallowing. If you cannot chew tablets completely, or if you have tooth disease, you may crush the tablets thoroughly before swallowing or discuss the oral powder formulation with your healthcare provider**
- Take LANTHANUM CARBONATE with or right after meals
- If you take an antacid medicine, take the antacid 2 hours before or 2 hours after you take LANTHANUM CARBONATE
- If you take medicine for your thyroid (levothyroxine), take the thyroid medicine 2 hours before or 2 hours after you take LANTHANUM CARBONATE
- If you take an antibiotic medicine, take the antibiotic 1 hour before or 4 hours after you take LANTHANUM CARBONATE

## **What are possible or reasonably likely side effects of LANTHANUM CARBONATE?**

See "**What is the most important information I should know about LANTHANUM CARBONATE?**"

The most common side effects of LANTHANUM CARBONATE include:

- nausea
- vomiting

- diarrhea
- stomach pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the side effects of LANTHANUM CARBONATE. For more information, ask your healthcare provider or pharmacist.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

#### **How should I store LANTHANUM CARBONATE?**

- Store LANTHANUM CARBONATE between 59°F to 86°F (15°C to 30°C).

**Keep LANTHANUM CARBONATE and all medicines out of the reach of children.**

#### **General information about LANTHANUM CARBONATE**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LANTHANUM CARBONATE for a condition for which it was not prescribed. Do not give LANTHANUM CARBONATE to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about LANTHANUM CARBONATE. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LANTHANUM CARBONATE that is written for healthcare professionals.

For more information call 1-800-828-2088.

#### **What are the ingredients in LANTHANUM CARBONATE?**

**Active ingredient:** lanthanum carbonate

**Inactive ingredients:** colloidal silicon dioxide NF, dextrates (hydrated) NF, and magnesium stearate NF.

**This Medication Guide has been approved by the US Food and Drug Administration.**

Distributed by:

**Prasco Laboratories**

Mason, OH 45040

Manufactured for **Shire US Inc.**, 300 Shire Way, Lexington, MA 02421.

Issued [11/2018]

#### **PRINCIPAL DISPLAY PANEL - 500 mg Tablet Bottle Package**

NDC 66993-422-85

PRASCO

**Lanthanum Carbonate  
chewable tablets**

**500 mg**

**Do not swallow tablets whole.**

**Chew or crush tablets completely before  
swallowing.**

**Take with or immediately after meals.**

2 bottles/45 chewable tablets each

**Rx only**

**Active Ingredient:** Each tablet contains 500 mg of lanthanum as lanthanum carbonate hydrate

**Inactive Ingredients:** Colloidal silicon dioxide, dextrates, and magnesium stearate.

**See package insert for full prescribing information.**

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

NDC 66993-422-85



# Lanthanum Carbonate

chewable tablets

**500 mg**

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

2 bottles/45 chewable tablets each  
Rx only

**Active Ingredient:** Each tablet contains 500 mg of lanthanum as lanthanum carbonate hydrate

**Inactive Ingredients:** Colloidal silicon dioxide, dextrates, and magnesium stearate.

**See package insert for full prescribing information.**  
Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]



### Information for patients:

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

Please follow your doctor's prescribing instructions.

**Information for Pharmacists:**  
Each patient package contains (2 bottles/45 tablets each) and is designed as one month's therapy. Packages should not be broken.

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Mason, OH 45040 USA  
Manufactured for: Shire US Inc.  
300 Shire Way, Lexington,  
MA 02421 USA © 2016  
Product of Italy  
015808  
22377v3

**500 mg**  
**PATIENT PACK ONE MONTH SUPPLY**

Lanthanum Carbonate  
chewable tablets

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

NDC 00993-422-85



30 669 423 JUN



Lanthanum Carbonate  
chewable tablets **500 mg**

Do not swallow tablets whole. Chew or crush tablets completely before swallowing. Take with or immediately after meals.

NDC 66993-422-85

2 bottles/  
45 chewable  
tablets each

Rx Only



NDC 66993-422-85

Lanthanum Carbonate  
chewable tablets **500 mg**

2 bottles/45 chewable tablets each

Rx only



**PRINCIPAL DISPLAY PANEL - 750 mg Tablet Bottle Package**

NDC 66993-423-85

PRASCO

**Lanthanum Carbonate  
chewable tablets**

**750 mg**

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

6 bottles/15 chewable tablets each  
**Rx only**

**Active Ingredient:** Each  
tablet contains 750 mg  
of lanthanum as lanthanum  
carbonate hydrate

**Inactive Ingredients:**



Colloidal silicon dioxide,  
dextrates, and magnesium  
stearate.

**See package insert for full  
prescribing information.**

Store at 25°C (77°F)

excursions permitted to

15-30°C (59-86°F)

[see USP Controlled Room  
Temperature]

NDC 66993-423-85



# Lanthanum Carbonate

chewable tablets

## 750 mg

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

6 bottles/15 chewable tablets each  
Rx only



**Active Ingredient:** Each tablet contains 750 mg of lanthanum as lanthanum carbonate hydrate

**Inactive Ingredients:** Colloidal silicon dioxide, dextrates, and magnesium stearate.

See package insert for full prescribing information. Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]



# Lanthanum Carbonate

chewable tablets

6 bottles/  
15 chewable  
tablets each  
**750 mg**  
Rx only

**Information for patients:**

**Do not swallow tablets whole.  
Chew or crush tablets completely before swallowing.  
Take with or immediately after meals.**

Please follow your doctor's prescribing instructions.

**Information for Pharmacists:**

Each patient package contains (6 bottles/15 tablets each) and is designed as one month's therapy. Packages should not be broken.

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Product of Italy

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22402v3

PATIENT PACK ONE MONTH SUPPLY

## 750 mg

# Lanthanum Carbonate

chewable tablets

NDC 66993-423-85



**Do not swallow tablets whole.  
Chew or crush tabs completely before  
swallowing.  
Take with or immediately after meals.**



# Lanthanum Carbonate

**Do not swallow tablets whole.  
Chew or crush tablets completely  
before swallowing.**

6 bottles/  
15 chewable  
tablets each



NDC 66993-423-85



## PRINCIPAL DISPLAY PANEL - 1000 mg Tablet Bottle Package

NDC 66993-424-85

PRASCO

**Lanthanum Carbonate  
chewable tablets**

**1000 mg**

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

9 bottles/10 chewable tablets each

**Rx only**

**Active Ingredient:** Each  
tablet contains 1000 mg  
of lanthanum as lanthanum  
carbonate hydrate

**Inactive Ingredients:**  
Colloidal silicon dioxide,  
dextrates, and magnesium  
stearate.

**See package insert for full  
prescribing information.**

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



NDC 66993-424-85



# Lanthanum Carbonate 1000mg chewable tablets

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

9 bottles/10 chewable tablets each  
Rx only



**Active Ingredient:** Each tablet contains 1000 mg of lanthanum as lanthanum carbonate hydrate

**Inactive Ingredients:** Colloidal silicon dioxide, dextrates, and magnesium stearate.

See package insert for full prescribing information. Store at 25° C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]



## Lanthanum Carbonate chewable tablets

9 bottles/10 chewable tablets each

**1000mg**  
Rx only

### Information for patients:

**Do not swallow tablets whole.  
Chew or crush tablets completely before swallowing.  
Take with or immediately after meals.**

Please follow your doctor's prescribing instructions.

### Information for Pharmacists:

Each patient package contains (9 bottles/10 tablets each) and is designed as one month's therapy. Packages should not be broken.

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Product of Italy  
015784 22403v3

PATIENT PACK ONE MONTH SUPPLY

**1000mg**

**Do not swallow tablets whole.  
Chew or crush tablets completely before  
swallowing.  
Take with or immediately after meals.**

Lanthanum Carbonate  
chewable tablets



NDC 66993-424-85



Do not swallow tablets whole.

9 bottles/

NDC 66993-424-85

Lanthanum Carbonate  
chewable tablets 1000mg

DO NOT SWALLOW TABLETS WHOLE.  
Chew or crush tablets completely  
before swallowing.  
Take with or immediately after  
meals.

10 chewable  
tablets each

Rx Only



NDC 66993-424-03

Lanthanum Carbonate  
chewable tablets

9 bottles/10 chewable tablets each

1000mg

Rx only

## LANTHANUM CARBONATE

lanthanum carbonate tablet, chewable

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:66993-422
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LANTHANUM CARBONATE (UNII: 490D9F069T) (LANTHANUM CATION (3+) - UNII:O7FU5X12W5)	LANTHANUM CATION (3+)	500 mg

### Inactive Ingredients

Ingredient Name	Strength
DEXTRATES (UNII: G263MI44RU)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

### Product Characteristics

<b>Color</b>	WHITE	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	18mm
<b>Flavor</b>		<b>Imprint Code</b>	S405;500
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66993-422-85	2 in 1 PACKAGE	08/30/2017	
1	NDC:66993-422-47	45 in 1 BOTTLE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021468	08/30/2017	

## LANTHANUM CARBONATE

lanthanum carbonate tablet, chewable

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:66993-423
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LANTHANUM CARBONATE (UNII: 490D9F069T) (LANTHANUM CATION (3+) - UNII:O7FU5X12W5)	LANTHANUM CATION (3+)	750 mg

### Inactive Ingredients

Ingredient Name	Strength
DEXTRATES (UNII: G263MI44RU)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

### Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	20mm
Flavor		Imprint Code	S405;750
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66993-423-85	6 in 1 PACKAGE	08/30/2017	
1	NDC:66993-423-53	15 in 1 BOTTLE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021468	08/30/2017	

## LANTHANUM CARBONATE

lanthanum carbonate tablet, chewable

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:66993-424
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LANTHANUM CARBONATE (UNII: 490D9F069T) (LANTHANUM CATION (3+) - UNII:O7FU5X12W5)	LANTHANUM CATION (3+)	1000 mg

### Inactive Ingredients

Ingredient Name	Strength
DEXTRATES (UNII: G263M44RU)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6B30)	

### Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	22mm
Flavor		Imprint Code	S405;1000
Contains			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66993-424-85	9 in 1 PACKAGE	08/30/2017	
1	NDC:66993-424-75	10 in 1 BOTTLE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021468	08/30/2017	

**Labeler** - Prasco Laboratories (065969375)



## Establishment

Name	Address	ID/FEI	Business Operations
Patheon Manufacturing Services LLC		079415560	ANALYSIS(66993-422, 66993-423, 66993-424) , LABEL(66993-422, 66993-423, 66993-424) , MANUFACTURE(66993-422, 66993-423, 66993-424) , PACK(66993-422, 66993-423, 66993-424)

## Establishment

Name	Address	ID/FEI	Business Operations
Corden Pharma Bergamo SpA		438743601	ANALYSIS(66993-422, 66993-423, 66993-424) , API MANUFACTURE(66993-422, 66993-423, 66993-424)

## Establishment

Name	Address	ID/FEI	Business Operations
Element Materials Technology Pharma US LLC		081315325	ANALYSIS(66993-422, 66993-423, 66993-424)

## Establishment

Name	Address	ID/FEI	Business Operations
Reading Scientific Services Ltd (RSSL)		293610085	ANALYSIS(66993-422, 66993-423, 66993-424)

## Establishment

Name	Address	ID/FEI	Business Operations
Triclinic Labs		017662237	ANALYSIS(66993-422, 66993-423, 66993-424)

## Establishment

Name	Address	ID/FEI	Business Operations
Microbac Laboratories, Inc.		178463126	ANALYSIS(66993-422, 66993-423, 66993-424)

## Establishment

Name	Address	ID/FEI	Business Operations
Reckitt Benckiser Healthcare International Ltd.		230780363	ANALYSIS(66993-422, 66993-423, 66993-424) , MANUFACTURE(66993-422, 66993-423, 66993-424)