

PRODUCT MONOGRAPH

 **FOSRENOL**^{®*}

lanthanum carbonate hydrate

Chewable tablets

250mg, 500mg, 750mg, 1000mg lanthanum as lanthanum carbonate hydrate

Phosphate binder

Shire Canada Inc.
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lanthanum carbonate hydrate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Chewable tablets / 250, 500, 750 and 1000mg	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

FOSRENOL (lanthanum carbonate hydrate) is indicated as a phosphate binding agent in patients with end stage renal disease on dialysis. Experience with therapy beyond 2 years is limited. The risk versus benefit from administration beyond two years should be carefully considered. (see **Warnings and Precautions - Bone, Pharmacokinetics – Distribution, and Clinical Trials – Bone Safety**)

Geriatrics (>65 years of age):

Of the total number of patients in clinical studies of FOSRENOL, 32% (538) were ≥ 65 years of age while 9.3% (159) were ≥ 75 years of age. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

Pediatrics (<18 years of age):

The safety and efficacy of FOSRENOL have not been established in children. (see **Warnings and Precautions**)

CONTRAINDICATIONS

FOSRENOL (lanthanum carbonate hydrate) is contraindicated in patients with:

- Bowel obstruction, ileus and fecal impaction.
- Hypophosphatemia.
- Hypersensitivity to lanthanum carbonate or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

See **Toxicology – Mutagenicity** and **Carcinogenicity** sections.

Gastrointestinal

The safety of FOSRENOL (lanthanum carbonate hydrate) in patients with acute peptic ulcer, ulcerative colitis or Crohn's disease has not been established. Caution should be used in patients with these conditions. Lanthanum is known to cause constipation (see ADVERSE DRUG REACTIONS – Clinical Trial Adverse Drug Reactions), therefore, caution should be exercised in patients predisposed to bowel obstruction (e.g., previous abdominal surgery, peritonitis, etc.).

Serious cases of gastrointestinal obstruction, ileus and fecal impaction have been reported in post-marketing follow-up of patients treated with FOSRENOL, some requiring surgery or hospitalization.

Risk factors for gastrointestinal obstruction identified from post-marketing reports include alteration in gastrointestinal anatomy (e.g., history of gastrointestinal surgery) and hypomotility disorders (e.g., constipation, ileus, diabetes). Some cases were reported in patients with no history of gastrointestinal disease.

Advise patients to chew the tablet completely to reduce the risk of serious adverse gastrointestinal events such as those described above.

Hepatic/Biliary/Pancreatic

No studies have been done in patients with hepatic impairment. Although lanthanum is not metabolized, it is excreted in the bile. Caution should be exercised in patients with hepatic impairment or biliary obstruction, as elimination of absorbed lanthanum may be reduced.

Bone

Tissue Deposition:

Tissue deposition of lanthanum has been shown with FOSRENOL in animal and human studies. In bone biopsies of patients treated with FOSRENOL for up to 4.5 years, rising levels of lanthanum were noted over time (see **Pharmacokinetics – Distribution**). There is no information on the re-distribution of lanthanum eliminated from bone into other tissues upon termination of lanthanum carbonate therapy.

The effect of iron or aluminum chelation on serum lanthanum released from bone has not been studied. Patients requiring chelation treatment who are taking FOSRENOL should be monitored closely.

Safety data exceeding 24 months are currently limited. The risk/benefit from longer-term administration should be carefully considered.

Long-term Effects:

There were no differences in the rates of fracture in patients treated with FOSRENOL compared to Standard Therapy* for up to 3 years. The duration of treatment exposure and time of observation in the clinical program is too short to conclude that FOSRENOL does not adversely affect bone quality or the risk for fracture or mortality beyond 3 years. (see **Clinical Trials – Bone Safety**)

Special Populations

Pregnant Women: No adequate and well-controlled studies have been conducted in pregnant women. The effect of FOSRENOL on the absorption of vitamins and other nutrients has not been studied in pregnant women. FOSRENOL is not recommended for use during pregnancy. (see **Toxicology – Reproduction and Teratology**)

Nursing Women: The excretion of lanthanum in milk has not been studied in animals. It is not known whether lanthanum is excreted in human breast milk. Therefore, the use of FOSRENOL in women who are breastfeeding is not recommended.

Geriatrics (>65 years of age): Of the total number of patients in clinical studies of FOSRENOL, 32% (538) were ≥ 65 years of age while 9.3% (159) were ≥ 75 years of age. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

Pediatrics (<18 years of age): The safety and efficacy of FOSRENOL have not been established in patients below the age of 18 years. 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 FOSRENOL in pediatric patients is not recommended.

* Standard Therapy: Patients randomized to Standard Therapy continued to take their prescribed binder at the optimal dose required to control their phosphate levels at ≤ 5.9 mg/dL. Patients were allowed to switch phosphate binders throughout the study and could also take a combination of binders in order to achieve optimal phosphate control.

Monitoring and Laboratory Tests

Patients should adhere to recommended diets in order to control phosphate and fluid intake. FOSRENOL is presented as a chewable tablet therefore avoiding the need to take additional fluid. Serum phosphate levels should be monitored and the dose of FOSRENOL titrated every 2-3 weeks until an acceptable serum phosphate level is reached, with regular monitoring thereafter.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Gastrointestinal symptoms including, but not limited to; nausea, vomiting, abdominal cramps and diarrhea were observed in patients taking FOSRENOL. These symptoms were less frequent when taking FOSRENOL with or immediately after food.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In three placebo-controlled studies in end stage renal disease (ESRD) patients, the most common adverse events for FOSRENOL were gastrointestinal events such as nausea and vomiting, and they generally abated over time with continued dosing. Adverse events that were more frequent ($\geq 5\%$ difference) in the FOSRENOL group are presented in the following table.

Table 1. Adverse Events that were More Common to FOSRENOL in Placebo-Controlled, Double-blind Studies with Treatment Periods of 4-6 Weeks		
Body System Preferred Terminology (WHOART)	FOSRENOL % (n=180)	Placebo % (n=95)
Dialysis Complication-NW Dialysis Graft Occlusion	7.8	1.1
Gastrointestinal System Disorders Abdominal Pain Nausea Vomiting	5.0 10.6 9.4	0.0 5.3 4.2

WHOART = World Health Organization Adverse Reactions Thesaurus,
 NW = non-WHOART term developed by Sponsor for the clinical development program

The safety of FOSRENOL was studied in two long-term clinical trials that included 1215 patients treated with FOSRENOL and 944 with alternative therapy. Sixteen percent (16%) of patients in these comparative, open-label studies discontinued in the FOSRENOL-treated group due to adverse events. Gastrointestinal adverse events, such as nausea, diarrhea and vomiting, were the most common type of event leading to discontinuation.

The number of withdrawals and the most common adverse events ($\geq 5\%$ in either treatment group) in both the long-term (2-year), open-label, active-controlled, study of FOSRENOL vs. alternative therapy (Study A) and the 6-month, comparative study of FOSRENOL vs. calcium carbonate (Study B) are shown in Table 2 and Table 3, respectively. In Table 3, Study A events have been adjusted for mean exposure differences between treatment groups (with a mean exposure of 1.0 year on lanthanum and 1.4 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.74.

Table 2. Number of Withdrawals/Phosphate Levels Achieved by Study Phase				
	Study A*		Study B**	
WITHDRAWALS				
	FOSRENOL	Alternative Therapy	FOSRENOL	Calcium Carbonate
Titration Phase	98/668 (14.67%)	38/670 (5.67%)	60/510 (11.96%)	41/257 (15.95%)
Maintenance Phase	374/570 (65.61%)	311/632 (49.21%)	188/450 (41.78%)	103/207 (49.76%)

Table 2. Number of Withdrawals/Phosphate Levels Achieved by Study Phase				
	Study A*		Study B**	
MEAN SERUM PHOSPHATE LEVEL ACHIEVED				
Titration Phase	6.43mg/dL* (2.06mmol/L)	5.71mg/dL* (1.85mmol/L)	1.87mmol/L **	1.66mmol/L **
Maintenance Phase	6.17mg/dL (1.97mmol/L)	6.05mg/dL (1.94mmol/L)	1.73mmol/L	1.72mmol/L

*Study A: Patients in the FOSRENOL group were titrated over a six-week period starting from a dose of 750mg/day and then maintained on doses up to 3000mg/day. The alternative therapy group started the titration phase at their optimal dose and were subsequently maintained at their optimal dose with the allowance of switching/adding phosphate binders if they wished.

**Study B: Patients in the FOSRENOL group were titrated from 375mg/day up to their optimal dose and then maintained on doses up to 3000mg/day. The calcium carbonate group started the titration phase at their optimal dose and were maintained on doses up to 9000mg/day.

Table 3. Incidence of Treatment-Emergent Adverse Events that Occurred in $\geq 5\%$ of Patients (in Either Treatment Group) and in Both Comparative Studies A and B				
	Study A %		Study B %	
	FOSRENOL (n=682)	Alternative* Therapy Adjusted Rates (n=677)	FOSRENOL (n=533)	Calcium Carbonate (n=267)
Nausea	37	29	16	13
Vomiting	27	22	18	11
Dialysis graft complication	25	24	3	5
Diarrhea	24	24	13	10
Headache	22	21	5	6
Dialysis graft occlusion	21	21	4	6
Abdominal pain	17	18	5	3
Hypotension	16	18	8	9
Constipation	15	14	6	7
Bronchitis	5	6	5	6
Rhinitis	4	6	7	6
Hypercalcemia	4	8	0	20

*Alternative Therapy: Patients randomized to alternative therapy continued to take their prescribed binder at the optimal dose required to control their phosphate levels at ≤ 5.9 mg/dL. Patients were allowed to switch phosphate binders throughout the study and could also take a combination of binders in order to achieve optimal phosphate control.

The dose range used in Study B was FOSRENOL 375mg-3000mg as elemental lanthanum and calcium carbonate 1500mg-9000mg elemental calcium.

Less Common Clinical Trial Adverse Events

In clinical studies, the following other, less common ($\geq 0.1\%$ and $< 5\%$), adverse drug reactions were reported:

Infections and infestations: gastroenteritis, laryngitis

Blood and lymphatic system disorders: eosinophilia

Endocrine disorders: hyperparathyroidism

Metabolism and nutrition disorders: anorexia, appetite increased, hyperglycemia, hyperphosphatemia, hypocalcemia, hypophosphatemia

Nervous system disorders: dizziness, taste alteration

Ear and labyrinth disorders: vertigo

Gastrointestinal disorders: dry mouth, dyspepsia, eructation, esophagitis, flatulence, gastrointestinal disorder NOS (not otherwise specified), indigestion, irritable bowel syndrome, loose stools, stomatitis, tooth disorder

Skin and subcutaneous tissue disorders: alopecia, erythematous rash, itching, pruritus, sweating increased

Musculoskeletal and connective tissue disorders: arthralgia, myalgia, osteoporosis

General disorders: asthenia, chest pain, fatigue, malaise, pain, peripheral edema, thirst

Investigations: alkaline phosphatase increased, blood aluminum increased, GGT increased, hepatic transaminases increased, weight decrease

Although there have been a number of additional isolated events reported, none of these were considered unexpected in this patient population.

In a comparative clinical study, patients on FOSRENOL had a lower incidence of hypercalcemic episodes relative to patients on calcium-based phosphate binder ($p < 0.001$).

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of FOSRENOL:

Gastrointestinal disorders: dyspepsia

General disorder: Tooth injury

Skin and subcutaneous tissue disorders: allergic skin reactions (including pruritus, skin rashes and urticaria)

DRUG INTERACTIONS

Overview

Lanthanum carbonate hydrate is not a substrate for cytochrome P450 and does not significantly inhibit the activities of the major human cytochrome P450 isoenzymes, CYP1A2, CYP2D6, CYP3A4, CYP2C9 or CYP2C19 in vitro.

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

Drug-Drug Interactions

In Vitro Drug Interactions:

Gastric Fluid: The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril) was investigated in simulated gastric fluid. The results suggest that precipitation in the stomach of insoluble complexes of these drugs with lanthanum is unlikely.

In Vivo Drug Interactions:

No effects of lanthanum were found on the absorption of digoxin (0.5mg), metoprolol (100mg), or warfarin (10mg) in healthy subjects co-administered lanthanum carbonate (three doses of 1000mg on the day prior to exposure and one dose of 1000mg on the day of co-administration). 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.

In healthy subjects, the absorption and pharmacokinetics of a single dose of 1000mg of FOSRENOL was unaffected by co-administration of citrate.

No effects of FOSRENOL on serum levels of 25-dihydroxy vitamin D3, vitamin A, vitamin B12, vitamin E and vitamin K were observed in patients who were monitored for 6 months.

Co-administration of FOSRENOL (1000mg tid for 1 day) with calcitriol (2 x 0.5µg) to healthy subjects did not significantly alter peak concentrations or overall extent of absorption of calcitriol (1,25-dihydroxyvitamin D3).

Co-administration of FOSRENOL with quinolone antibiotics may reduce the extent of their absorption as a result of complex formation. The bioavailability of oral ciprofloxacin was decreased by approximately 50% when taken with FOSRENOL in a single dose study in healthy volunteers. FOSRENOL should not be taken simultaneously with oral quinolone antibiotics.

The bioavailability of levothyroxine was decreased by approximately 40% when taken together with FOSRENOL. FOSRENOL should not be taken simultaneously with thyroid hormones replacement therapy and closer monitoring of TSH levels is recommended in patients receiving both medicinal products.

Other Possible Interactions:

Interactions with drugs such as tetracycline and doxycycline are theoretically possible. If these compounds are to be co-administered, it is recommended that they not be taken within 2 hours of dosing with FOSRENOL.

There is a potential for FOSRENOL to interact with compounds which bind to cationic antacids (e.g., aluminium-, magnesium-, or calcium-based). It is recommended that compounds known to interact with antacids should not be taken within 2 hours of dosing with FOSRENOL (e.g., chloroquine, hydroxychloroquine and ketoconazole).

No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

The drug interactions profile of FOSRENOL is characterized by the potential of lanthanum to bind to drugs with anionic functions (e.g., carboxyl, carbonyl and hydroxyl groups). When administering any such medications where a reduction in the bioavailability of that medication would have a clinically significant effect on safety or efficacy, the physician should consider dosing that medicine apart from FOSRENOL or monitoring blood levels.

Drug-Herb Interactions

Interactions of FOSRENOL with herbs have not been established.

Drug-Laboratory Interactions

Abdominal X-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent.

Drug-Lifestyle Interactions

Interactions of FOSRENOL with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Serum phosphorus levels should be monitored as needed during titration until an optimal serum phosphorus level is reached, and then on a regular basis thereafter.

Recommended Dose and Dosage Adjustment

The recommended initial daily dose of FOSRENOL (lanthanum carbonate hydrate) for adults is 750mg-1500mg. The dose should be titrated every 2-3 weeks to a level that achieves maintenance of acceptable serum phosphorus levels. The daily dose should be divided and taken with or immediately after meals. Patients should adhere to recommended diets in order to control phosphate and fluid intake. FOSRENOL is presented as a chewable tablet, therefore avoiding the need to take additional fluid.

In clinical studies in ESRD patients, FOSRENOL doses up to 3750mg were evaluated. Most patients required a total daily dose between 1500 and 3000mg of FOSRENOL to reduce serum phosphorus levels to less than 6.0mg/dL (1.92mmol/L). Doses were generally titrated in increments of 750mg/day.

Missed Dose

A missed dose should be taken at the next scheduled dose with a meal. Taking a dose at a time other than mealtime may lead to nausea and vomiting. Patients should not double-up the dose to catch up.

Administration

Tablets should be chewed completely before swallowing. Intact tablets should not be swallowed.

OVERDOSAGE

The highest daily dose of lanthanum carbonate administered to healthy adult subjects during a phase I study was 9000mg/day for 3 days. The symptoms associated with overdose are adverse reactions such as headache, nausea and vomiting. Given the local activity of FOSRENOL in the gut, and the excretion in feces of the majority of the dose, supportive therapy is recommended in case of overdosage. Lanthanum carbonate was not acutely toxic in animals by the oral route (see **TOXICOLOGY – Acute and Subacute Toxicity**).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Patients with ESRD can develop hyperphosphatemia as a result of phosphorus retention, which may be associated with secondary hyperparathyroidism and elevated calcium phosphate product.

Treatment of hyperphosphatemia 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.

Mechanism of Action

FOSRENOL (lanthanum carbonate hydrate) acts in the lumen of the gut to bind dietary phosphorus released from food during digestion. Lanthanum carbonate hydrate inhibits the absorption of phosphorus by the formation of highly insoluble lanthanum phosphate complexes that cannot easily pass through the wall of the gastrointestinal tract, and are excreted in the feces.

Pharmacodynamics

Lanthanum carbonate dissociates in the acid environment of the upper GI tract to release lanthanum ions that bind dietary phosphate released from food during digestion. FOSRENOL inhibits absorption of phosphate by forming highly insoluble lanthanum phosphate complexes, consequently reducing both serum phosphate and calcium phosphate product.

In vitro studies have shown that in the physiologically relevant pH range of 3 to 5 in gastric fluid, lanthanum binds approximately 97% of the available phosphate when lanthanum is present in a two-fold molar excess to phosphate. In order to bind dietary phosphate efficiently, lanthanum should be administered with or immediately after a meal.

Pharmacokinetics

Since the binding of dietary phosphorus occurs in the lumen of the stomach and upper small intestine, plasma lanthanum concentrations are not predictive of lanthanum carbonate hydrate's efficacy.

Absorption:

Following single- or multiple- dose oral administration of FOSRENOL to healthy subjects, the concentration of lanthanum in plasma was very low, with oral bioavailability estimated to be <0.002%.

In healthy subjects, plasma AUC and C_{max} increased as a function of dose, but in a less than proportional manner, after single oral doses of 250 to 1000mg lanthanum, consistent with dissolution-limited absorption. The apparent plasma elimination half-life in healthy subjects was 36 hours.

In renal dialysis patients dosed for 10 days with 1000mg lanthanum carbonate hydrate three times daily, the mean (\pm sd) lanthanum C_{max} was 1.06 (\pm 1.04) ng/mL, and the mean AUC_{last} was 31.1 (\pm 40.5) ng·h/mL. During long-term administration (52 weeks) in renal dialysis patients, the mean lanthanum concentration in plasma was approximately 0.6ng/mL. Regular blood level

monitoring in renal dialysis patients taking lanthanum carbonate hydrate (with increasing doses within the therapeutic dose range) for up to 2 years showed minimal increase in plasma lanthanum concentrations over this time period.

The effect of food on the bioavailability of FOSRENOL has not been evaluated, but 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.

Distribution:

Lanthanum is present in the environment. Measurement of background levels in non-lanthanum carbonate-treated ESRD patients on dialysis during Phase III clinical trials revealed concentration of <0.05 to 0.90ng/mL in plasma, and <0.006 to 1.0µg/g in bone biopsy samples.

In vitro, lanthanum is highly bound (>99%) to human plasma proteins, including human serum albumin, α1-acid glycoprotein, and transferrin. Binding to erythrocytes in vivo is negligible in rats.

In long-term studies in mice, rats and dogs, absorbed lanthanum was widely distributed to systemic tissues, predominantly bone, liver and the gastrointestinal tract, including the mesenteric lymph nodes. Lanthanum concentrations in several tissues, including the gastrointestinal tract, bone and liver, increased over time and were several orders of magnitude higher than plasma concentrations. Changes in tissue lanthanum levels after withdrawal of treatment varied between tissues. A relatively high proportion of lanthanum was retained in tissues for longer than 6 months after cessation of dosing [median percent retained in bone ≤100% (rat) and ≤87% (dog) and in the liver ≤6% (rat) and ≤82% (dog). There is no evidence from animal studies that lanthanum crosses the blood-brain barrier.

In 105 bone biopsies from patients treated with FOSRENOL for up to 4.5 years, rising levels of lanthanum were noted over time. Steady-state bone concentrations were not reached during the period studied (see **Clinical Trials – Bone Safety**). No clinical data are available on deposition of lanthanum in other tissues in humans, including liver and gastrointestinal tract.

Metabolism:

Lanthanum carbonate is not metabolized and is not a substrate of CYP450. In vitro metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40µg/mL does not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, C9, 2C19, 2D6 and 3A4).

Excretion:

Lanthanum was cleared from plasma following discontinuation of therapy with an elimination half-life of 53 hours.

No information is available regarding the mass balance of lanthanum in humans after oral administration. In healthy subjects, the majority of an orally administered dose was excreted in the feces with only around 0.000031% of the oral dose excreted in the urine (representing <2% of total plasma clearance).

Studies in chronic renal failure patients with hepatic impairment have not been conducted. In patients with co-existing hepatic disorders at the time of entry into Phase III clinical studies, there was no evidence of increased plasma exposure to lanthanum or worsening hepatic function after treatment with FOSRENOL for periods up to 2 years.

Paired bone biopsies from 11 patients were collected after 12 months of lanthanum carbonate treatment and 24-26 months after stopping lanthanum carbonate treatment. The mean bone lanthanum concentration at the end of the treatment period was 2806µg/kg (range 530 to 5513µg/kg) and the mean concentration was 1903µg/kg (range 543 to 5683µg/kg) after 24-26 months off-treatment. This limited data demonstrated that lanthanum is slowly cleared from bone. Its clearance showed considerable variability between individuals.

STORAGE AND STABILITY

Store between 15-25°C; excursions permitted up to 30°C. Protect from moisture. Keep in a safe place out of the reach of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FOSRENOL is supplied as a chewable tablet in four dosage strengths for oral administration: 250mg tablets, 500mg tablets, 750mg tablets and 1000mg tablets. Each chewable tablet is white to off-white, round, flat with a beveled edge, and embossed on one side with 'S405' and the dosage strength corresponding to the content of the elemental lanthanum.

FOSRENOL 250mg chewable tablets are supplied in bottles of 90 and 400 tablets.

FOSRENOL 500mg chewable tablets are supplied in bottles of 45 tablets.

FOSRENOL 750mg chewable tablets are supplied in bottles of 15 tablets.

FOSRENOL 1000mg chewable tablets are supplied in bottles of 10 tablets.

Each chewable tablet of FOSRENOL (lanthanum carbonate hydrate) contains either 250, 500, 750 or 1000mg of elemental lanthanum (as lanthanum carbonate hydrate) and the following non-medicinal ingredients: colloidal silicon dioxide, dextrans (hydrated), and magnesium stearate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: lanthanum carbonate hydrate

Chemical name: lanthanum (III) carbonate hydrate

Molecular formula and molecular mass:

FOSRENOL contains lanthanum carbonate (2:3) hydrate with molecular formula $\text{La}_2(\text{CO}_3)_3 \cdot q\text{H}_2\text{O}$ (on average $q=4$ to 5 moles of water) and a molecular mass of 457.8 (anhydrous).

Physicochemical properties:

Lanthanum carbonate hydrate, a white to almost white powder, is a basic carbonate consisting primarily of carbonate tetrahydrate, $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$, although other lanthanum hydrates may be present with on average 4 to 5 moles of bound water. A macromolecular structure is formed from the association of water molecules across the crystal lattice. The pKa values for its salt, carbonic acid, are 10.33 and 6.35. Lanthanum carbonate is insoluble in organic solvents. Aqueous solubility at a pH of 1.2 is between 5 and 10mg/mL, and is poor at alkaline pHs.

CLINICAL TRIALS

Study demographics and trial design

The effectiveness of FOSRENOL 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.

Double-Blind, Placebo-Controlled Studies

One-hundred-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 225mg (n=27), 675mg (n=29), 1350mg (n=30) or 2250mg (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.

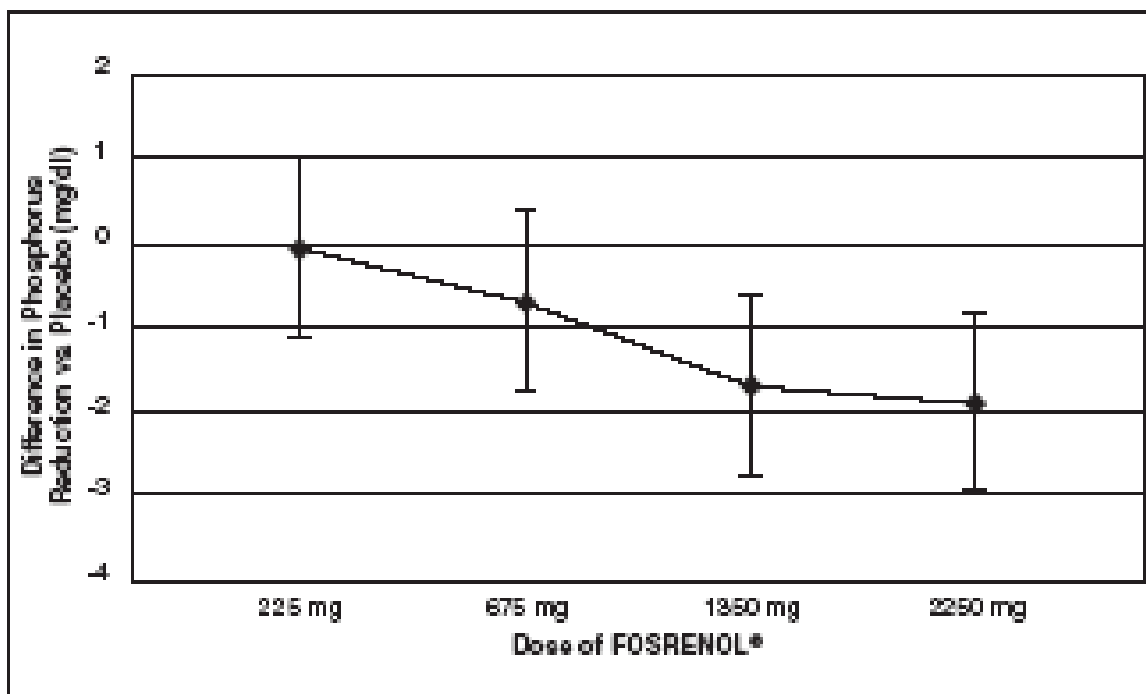
Fifty-four subjects [37 (33%) patients on FOSRENOL and 17 (53%) patients on placebo] withdrew from the study after randomization. The reasons for discontinuation are described in Table 4 below.

Table 4. Reasons for Discontinuation in Study LAM-204		
Reason for Discontinuation	FOSRENOL (n=112 randomized)	Placebo (n=32 randomized)
Total withdrawn	37 (33%)	17 (53%)
Adverse events, including death	10 (9%)	3 (9%)
Outside pre-specified safety criteria*	19 (17%)	13 (41%)
Administrative or other	8 (7%)	1 (3%)

* Including efficacy-related criteria such as $PO_4 > 10\text{mg/dL}$, $PO_4 \times Ca > 80\text{mg}^2/\text{dL}^2$, and change in PTH $> 500\text{pg/mL}$.

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 FOSRENOL and Placebo Group in a 6-Week, Dose-ranging, Double-blind Study in ESRD Patients (with 95% Confidence Intervals)



One-hundred-eighty-five patients with ESRD 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 a four- to six-week titration of lanthanum carbonate to achieve a goal phosphate level between 4.2 and 5.6mg/dL in one study (doses up to 2250mg/day) or ≤ 5.9 mg/dL in the second study (doses up to 3000mg/day) and maintenance through 6 weeks, patients were randomized to lanthanum or placebo.

Fifty (27%) of the subjects taking lanthanum in the titration phase withdrew (unplanned) from the studies prior to randomization. The reasons for discontinuation were: adverse event including 1 death (16; 8.6%), outside pre-specified safety criteria (14; 7.6%), and protocol violation or other (20; 10.8%).

During the placebo-controlled, randomized withdrawal phase (four weeks), the phosphorus concentration rose in the placebo group by 1.9mg/dL in both studies relative to patients who remained on lanthanum carbonate therapy.

Open-Label, Active-Controlled Studies

Two long-term, open-label studies were conducted, involving a total of 2159 patients with ESRD undergoing hemodialysis. In Study LAM-301, 800 patients completed a washout period off phosphate binders (Part 1) and were then randomized 2:1 to receive either FOSRENOL or calcium carbonate. These patients were then dose-titrated to a target phosphate level of ≤ 1.8 mmol/L over a five-week period (Part 2). On completion of titration, remaining patients remained on their randomized phosphate binder and were followed for six months (Part 3). After the six-month maintenance phase, all subjects who had been randomized were eligible to take part in a longer-term extension on FOSRENOL only. The purpose of the extension was primarily to assess safety and long-term tolerability of FOSRENOL.

Of the 767 subjects who entered the titration period (ITT population), 101 [FOSRENOL: 60 (11.8%); Calcium: 41 (16.0%)] withdrew before entering the maintenance phase of the study. Two-hundred and ninety-one subjects [FOSRENOL: 188 (41.8%); Calcium: 103 (49.8%)] withdrew during the maintenance phase (to end of Part 3). A total of 375 subjects (including those who re-entered the study at the beginning of the extension) completed the six-month randomized therapy and additional six-month open-label safety extension. The reasons for discontinuation are shown in Table 5.

Table 5. Reasons for Discontinuation in Study LAM-301		
Reason for Discontinuation	FOSRENOL (n=533 randomized)	Calcium (n=267 randomized)
Total withdrawn	271 (50.8%)	154 (57.7%)
Death	19 (3.6%)	11 (4.1%)
Adverse event	82 (15.4%)	47 (17.6%)
Serious adverse event	12 (2.3%)	4 (1.5%)
Protocol violation	24 (4.5%)	11 (4.1%)
Withdrew consent	43 (8.1%)	29 (10.9%)
Received kidney transplant	23 (4.3%)	16 (6.0%)
Lost to follow-up	5 (0.9%)	1 (0.4%)
Other (including 1 missing)	64 (12.0%)	34 (12.7%)

At the end of the maintenance phase of the study, the mean phosphate level was 1.73mmol/L (representing -0.74mmol/L from baseline) in the FOSRENOL group (doses up to 3000mg/day), and 1.73mmol/L (representing -0.75mmol/L from baseline) in the Calcium group (doses up to 9000mg/day) in patients who completed the maintenance period.

In Study LAM-307, 1359 patients were randomized to receive either FOSRENOL or Standard Therapy*. Subjects completed a three-week washout period (Part 1) off all phosphate binders. After a subsequent titration period of six weeks (Part 2), the patients were maintained on their randomized treatment for 24 months (Part 3). A total of 682 patients were randomized to FOSRENOL therapy, and 677 were randomized to Standard Therapy*.

Of the 1359 patients who entered the titration period, 842 (62%) withdrew prior to completion of the two-year study. Of these, 486 (71.3%) were in the FOSRENOL group and 356 (52.6%) were in the Standard Therapy* group.

The reasons for discontinuation are shown in Table 6.

* Standard Therapy: Patients randomized to Standard Therapy continued to take their prescribed binder at the optimal dose required to control their phosphate levels at ≤ 5.9 mg/dL. Patients were allowed to switch phosphate binders throughout the study and could also take a combination of binders in order to achieve optimal phosphate control.

Table 6. Reasons for Discontinuation in Study LAM-307		
Reason for Discontinuation	FOSRENOL (n=682 randomized)	Standard Therapy* (n=677 randomized)
Total withdrawn	486 (71.3%)	356 (52.6%)
Death**	42 (6.2%)	96 (14.2%)
Adverse event	98 (14.4%)	29 (4.3%)
Exceeded pre-specified safety criteria:		
Two PO ₄ > 10mg/dL	32 (4.7%)	22 (3.3%)
Two PO ₄ < 2.0mg/dL	0	2 (0.3%)
Two CaXPO ₄ > 90mg ² /dL ²	14 (2.1%)	7 (1.0%)
Calcium > 11.5mg/dL	2 (0.3%)	1 (0.1%)
Increase PTH > 500pg/mL	5 (0.7%)	1 (0.1%)
Protocol violation	13 (1.9%)	5 (0.7%)
Withdrew consent	107 (15.7%)	34 (5.0%)
Patient received kidney transplant	55 (8.1%)	75 (11.1%)
Lost to follow-up	10 (1.5%)	12 (1.8%)
Other	109 (16.0%)	73 (10.8%)

* Standard Therapy: Patients randomized to Standard Therapy continued to take their prescribed binder at the optimal dose required to control their phosphate levels at ≤ 5.9 mg/dL. Patients were allowed to switch phosphate binders throughout the study and could also take a combination of binders in order to achieve optimal phosphate control.

** Represents End of Study entry as the investigator-determined reason for study withdrawal. There were patients who died after study termination (13 FOSRENOL; 19 Standard Therapy). As a result, the total number of patients who died whether during the study or within 30 days after the last dose of study drug was 178, who are not represented all on this table.

Study LAM-307 was primarily a safety and tolerability study; phosphate control was a secondary objective.

One-hundred and sixty-one patients entered a further 12-month extension study, taking FOSRENOL only, to a total of three years. Of the 90 patients who completed the third year of therapy, 49 (54.4%) had a phosphate level better than the target of 1.8mmol/L.

No effects of FOSRENOL on serum levels of 25-dihydroxy vitamin D3, vitamin A, vitamin B12, vitamin E and vitamin K were observed in patients who were monitored for 6 months.

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 FOSRENOL or alternative therapy was 6.6%.

Bone Safety

Lanthanum Deposition in Bone

In the comparative bone studies, a trend towards increasing bone lanthanum concentrations with time in the Standard Therapy* group was observed from averaged data, the median rising 3-fold from a baseline of 53 μ g/kg (wet weight) at 24 months. In patients treated with lanthanum carbonate, the bone lanthanum concentrations increased during the first 12 months of lanthanum carbonate treatment up to a median of 1328 μ g/kg (range 122-5513 μ g/kg). Median and range concentrations at 18 and 24 months were similar to 12 months. The median at 54 months was 4246 μ g/kg (range 1673-9792 μ g/kg), a 3-fold increase from that at 12 months. Steady state bone concentrations were not reached during the period.

Bone Histology

Paired bone biopsies (at baseline and at one year) were collected from 63 patients randomized to either FOSRENOL (n=33) or calcium carbonate (n=30) in one study. In a second randomized study 99 patients had both a baseline and follow up biopsy after 1 or 2 years of treatment; 63 patients had bone biopsies at baseline and 1 year (FOSRENOL: n=31, Standard Therapy*: n=32), and 52 patients had biopsies at baseline and 2 years (FOSRENOL: n=31, Standard Therapy*: n=21). Histomorphometric analysis showed no differences in the development of mineralization defects between the groups up to 2 years. However, long-term effects of lanthanum on bone quality are unknown.

DETAILED PHARMACOLOGY

Preclinical

Pharmacodynamics

In vitro studies have shown that lanthanum carbonate has low aqueous solubility (<0.01mg/mL at pH 7.5). Furthermore, lanthanum binds with phosphorus to form an insoluble lanthanum phosphate complex. Therefore, lanthanum poses a low potential for gastrointestinal absorption.

Pharmacokinetics

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. Only a small amount was excreted in urine. In bile-duct cannulated rats, biliary excretion of intravenous lanthanum (administered as the soluble lanthanum chloride) was the predominant route of elimination.

There is no evidence from animal studies that lanthanum crosses the blood brain barrier.

* Standard Therapy: Patients randomized to Standard Therapy continued to take their prescribed binder at the optimal dose required to control their phosphate levels at \leq 5.9mg/dL. Patients were allowed to switch phosphate binders throughout the study and could also take a combination of binders in order to achieve optimal phosphate control.

TOXICOLOGY

Acute and Subacute Toxicity

The acute and subacute toxicological studies were conducted on two different compounds, lanthanum carbonate and lanthanum chloride. The reason for this is that lanthanum carbonate is basically insoluble, whereas lanthanum chloride is highly soluble. As such, it could present a vision of potential issues which may arise over time.

In single-dose oral toxicity studies in CD-1 mice and Sprague-Dawley rats, lanthanum carbonate at doses up to 2000mg/kg resulted in no deaths and produced no direct signs of toxicity. In single-dose intravenous toxicity studies in mice and rats, lanthanum chloride administered at 3.0 and 6.25mg/kg, the maximum non-lethal dose respectively, caused histopathological changes in the liver (including degeneration and necrosis of the hepatocytes, with hemorrhage and inflammation 2 to 5 days post-dose).

In two-week oral toxicity studies in CD-1 mice, Sprague-Dawley rats, and Beagle dogs, lanthanum carbonate at doses up to 2000mg/kg/day produced no deaths and did not result in any evidence of toxicity, although an increase in urine pH was observed in the lanthanum-treated rats and isolated incidences of pale feces and vomiting were observed in dogs at 1000 and 2000mg/kg/day.

Long-term Toxicity

In a 13-week oral toxicity study in CD-1 mice, lanthanum carbonate at doses up to 2000mg salt/kg/day produced no deaths. Evidence of localized reaction in the stomach (epithelial hyperplasia/hyperkeratosis of the limiting ridge, epithelial hyperplasia of the non-glandular region and mucosal inflammatory cell infiltration in the glandular region) and liver (accentuated lobular pattern/centrolobular hepatocyte hypertrophy) were observed at doses of 500, 1500 and 2000mg salt/kg/day. There was a dose-dependent accumulation of lanthanum particularly in the liver and femur.

In 13- and 26-week oral toxicity studies in Sprague-Dawley rats, the stomach was the target organ of lanthanum toxicity. Abnormal shape of the glandular region of the stomach was noted in females receiving 2000mg/kg/day in the 13-week study. In the 26-week study, microscopic findings of glandular stomach submucosal inflammation and mineralization and localized cellular hyperplasia of the stomach were observed in animals dosed at 600 and 2000mg/kg/day. No deaths were considered to be related to the toxicity of the drug in either study.

In Beagle dogs, oral (capsule) administration of lanthanum carbonate at doses up to 2000mg/kg/day for periods of up to 52 weeks was associated with fecal changes, increased urinary pH, and decreased urinary and plasma phosphate levels but otherwise produced no toxicologically significant changes in clinical, biochemical, or pathological observations. No mortalities occurred during the treatment period. There was a dose-related increase in lanthanum concentration in the femur at the end of the 52-week treatment period.

Long-term toxicity studies conducted using lanthanum chloride (intravenous) in both the rat and the dog showed considerable discrepancy in the toxicity of the two lanthanum salts. Lanthanum carbonate had no evidence of toxicity at 2000mg/kg/day, even for periods up to 52 weeks in dogs, while lanthanum chloride at a dose of 1mg/kg/day for 4 weeks in dogs resulted in chronic hepatitis.

Mutagenicity

Lanthanum carbonate tested negative for mutagenic activity in an in vitro Ames assay using *Salmonella typhimurium* and *Escherichia coli* strains and an in vitro HGPRT gene mutation and chromosomal aberration assays in Chinese Hamster Ovary (CHO) cells. Lanthanum carbonate also tested negative in an in vivo mouse micronucleus assay at oral doses up to 2000mg/kg/day.

In addition, lanthanum chloride was concluded to be non-clastogenic in a bone marrow micronucleus test in Sprague-Dawley rats and an unscheduled DNA synthesis assay in Han Wistar rats that were given IV lanthanum chloride at doses up to 0.1mg/kg/day, a dose that produced lanthanum concentrations >2000 times the peak human plasma concentration.

Carcinogenicity

Oral administration of lanthanum carbonate to Sprague-Dawley rats for up to 104 weeks, at doses up to 1500mg/kg/day, revealed no evidence of carcinogenic potential. In CD-1 mice, oral administration of lanthanum carbonate for up to 99 weeks was associated with an increased incidence of glandular stomach adenomas in male mice in the high-dose group (1500mg/kg/day).

Reproduction and Teratology

Lanthanum carbonate hydrate was evaluated for effects on embryofetal development in Sprague-Dawley rats (segment I and segment III) and in rabbits (segment II) following oral administration. In the segment I study, lanthanum carbonate hydrate was not embryotoxic or teratogenic at doses up to 2000mg/kg/day. There was an increased incidence of observations of small pups in the group treated at 2000mg/kg/day. In the segment II study, oral administration of lanthanum carbonate hydrate at 1500mg/kg/day in rabbits was associated with a reduction in maternal body weight gain, food consumption and fecal production, increased pre- and post-implantation loss, reduced fetal weights, and delayed fetal ossification.

In the segment III pre- and post-natal study, lanthanum carbonate hydrate was administered to rats during pregnancy and lactation at 200, 600 or 2000mg/kg/day. At the highest dose, there was a reduction in pup bodyweight, delayed eye opening, and delayed female sexual development (preputial separation and vaginal opening) observed in the offspring.

Lanthanum carbonate at doses up to 2000mg/kg/day did not affect fertility or mating performance of male or female Sprague-Dawley rats.

Lanthanum Accumulation in Tissues

Studies in animals have shown deposition of lanthanum in tissues, mainly the gastrointestinal tract, mesenteric lymph nodes, liver and bone (see also **Pharmacokinetics – Distribution**). Pre-clinical studies also found that chronically renal impaired rats given high doses of lanthanum carbonate resulted in osteomalacia, and non-dietary phosphate supplements minimized this effect.

Immunotoxicity


Specific immunotoxicity studies have not been performed.

REFERENCES

1. AL-Baaj F, Speake M, Hutchison AJ. Control of serum phosphate by oral lanthanum carbonate in patients undergoing hemodialysis and continuous ambulatory peritoneal dialysis in a short-term, placebo-controlled study. *Nephrol Dial Transplant* 2005; 20: 775-82.
2. Behets GJ, Dams G, Vercauteren SR, Damment SJ, Bouillon R, De Broe ME, D' Haese PC. Does the phosphate binder lanthanum carbonate affect bone in rats with chronic renal failure? *J Am Soc Nephrol* 2004; 15: 2219-28.
3. Damment SJ, Pennick M. Clinical pharmacokinetics of the phosphate binder lanthanum carbonate. *Clin Pharmacokinet*. 2008;47(9):553-63. Review.
4. Damment SJP, Shen V. Assessment of effects of lanthanum carbonate with and without phosphate supplementation on bone mineralization in uremic rats. *Clin Nephrol* 2005;67:127-37.
5. David S, Cambi V. Haemodialysis and peritoneal dialysis. *Medicine* 1995;23:151-5.
6. D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S, et al. A multi-centre study on the effects of lanthanum carbonate (FOSRENOL) and calcium carbonate on renal bone disease in dialysis patients. *Kidney Int* 2003;63(Suppl 85):S73-8.
7. Finn WF, Joy MS, Hladik G and Lanthanum Study group. Efficacy and safety of lanthanum carbonate for reduction of serum phosphorus in patients with chronic renal failure receiving hemodialysis. *Clin Nephrol* 2004;62:193-201.
8. Freemont T, Malluche HH. Utilization of bone histomorphometry in renal osteodystrophy: demonstration of a new approach using data from a prospective study of lanthanum carbonate. *Clin Nephrol* 2005; 63: 138-45.
9. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO_4 , $\text{Ca} \times \text{PO}_4$ product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001;12:2131-8.
10. Graff L, Burnel D. A possible non-aluminum oral phosphate binder? A comparative study on dietary phosphorus absorption. *Res Commun Mol Path Pharmacol* 1995;89 373-88.
11. Hanioka N, Jinno H, Sekita H, Toyo'oka T, Ando M, Kojima S, Takeda M. Metabolism of calcium and phosphorus in rats after continuous oral administration of lanthanum. *Jpn J Toxicol Environ Health* 1994; 40:26-33.
12. How PP, Fischer JH, Arruda JA and Lau AH. Effect of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. *Clin J Am Soc Nephrol* 2007;2:1235-40.

13. Hutchison AJ, Speake M, Al-Baaj F. Reducing high phosphate levels in patients with chronic renal failure undergoing dialysis: a 4-week, dose-finding, open-label study with lanthanum carbonate. *Nephrol Dial Transplant* 2004;19:1902-6.
14. Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R et al. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate. *Nephron Clin Pract* 2005;100:8-19.
15. Joy MS, Finn WF and Lanthanum Study Group. Randomized, double-blind, placebo-controlled, dose-titration, Phase III study assessing the efficacy and tolerability of lanthanum carbonate: a new phosphate binder for the treatment of hyperphosphatemia. *Am J Kidney Dis* 2003;46:96-107.
16. Weitzman SP, Ginsburg KC and Carlson HE. Colesevelam hydrochloride and lanthanum carbonate interfere with the absorption of levothyroxine. *Thyroid* 2009;19:77-9.
17. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. Salmonella mutagenicity tests: V. Results from testing of 311 chemicals. *Env and Mol Mut* 1992;19:2-141.

PART III: CONSUMER INFORMATION


FOSRENOL^{®*}
 (lanthanum carbonate hydrate)

This leaflet is Part III of a three-part "Product Monograph" published when FOSRENOL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FOSRENOL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

- To reduce phosphorus levels in patients with end stage renal disease who are on dialysis.

What it does:

FOSRENOL reduces the absorption of phosphate from food by binding the phosphate in the gut.

When it should not be used:

You should not take FOSRENOL

- If you have blocked bowels.
- If you have severe constipation.
- You have low blood phosphate levels (hypophosphatemia).
- If you are allergic to any of the ingredients in FOSRENOL (see "What the medicinal ingredient is" and "What the important non medicinal ingredients are").

What the medicinal ingredient is:

Lanthanum carbonate hydrate

What the important nonmedicinal ingredients are:

Colloidal silicon dioxide, dextrates (hydrated) and magnesium stearate.

What dosage forms it comes in:

Chewable Tablets. Each chewable Tablet contains 250mg, 500mg, 750mg or 1000mg of lanthanum as lanthanum carbonate hydrate.

WARNINGS AND PRECAUTIONS

BEFORE you use FOSRENOL talk to your doctor or pharmacist if:

- You have a history of bowel blockage, ileus, constipation, or diabetes
- You have had previous abdominal surgery
- You have suffered from peritonitis (inflammation of the abdomen)
- You suffer from acute peptic ulcer, ulcerative colitis, or Crohn's disease
- You suffer from liver impairment or biliary obstructions

- You are taking chelation therapy
- You are pregnant, planning to get pregnant or nursing.

Tell your doctor that you are taking FOSRENOL before having an X-ray of your stomach (abdomen), as this may affect the results.

You should also be aware that:

- FOSRENOL is not for use in children under 18 years of age
- Experience with therapy beyond 2 years is limited
- Bone lanthanum accumulation has been shown in animals and humans.

INTERACTIONS WITH THIS MEDICATION

Drugs known to interact with antacids should not be taken within 2 hours before or after taking FOSRENOL (e.g., tetracycline, doxycycline, chloroquine, hydroxychloroquine and ketoconazole).

It is not recommended that you take oral floxacin antibiotics (including ciprofloxacin) simultaneously with FOSRENOL.

If you are taking thyroxine (for an underactive thyroid), do not take it simultaneously with FOSRENOL; your doctor may want to monitor blood levels of thyroid-stimulating hormone (TSH) more closely.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines even those not prescribed.

PROPER USE OF THIS MEDICATION**Usual Dose:**

Usual starting daily dose is between 750mg to 1500mg, to be taken in divided doses and with or immediately after a meal. The dose may be adjusted every 2 to 3 weeks. Most patients require a daily dose between 1500mg and 3000mg.

The tablet should be chewed completely before swallowing. Do not swallow tablets whole.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, then take the next scheduled dose at your following meal. Taking a dose at a time other than mealtime may lead to nausea and vomiting. Do not double dose to catch up.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common adverse events in clinical trials were gastrointestinal such as nausea and vomiting.

You may also experience:

Dialysis graft complications, indigestion or heartburn, diarrhea or soft stool, headache, constipation, respiratory infection, infection of the throat, infection of the membrane of the nose, high blood sugar levels, low or high blood phosphate levels, loss of appetite, increased appetite, dizziness, strange tastes, trouble with digestive system, gas, dry mouth, difficulty swallowing, sores in the mouth, tooth disorder, tooth injury, losing some hair, itching, redness of skin, rash, increased sweating, muscle and joint pain, fatigue, malaise, pain, thirst, increased liver enzyme levels, increased blood aluminium levels, and weight decrease.

To reduce side effects such as nausea, vomiting, abdominal cramps and diarrhea, take FOSRENOL with or immediately after a meal.

HOW TO STORE IT

Store between 15-25°C; excursions permitted up to 30°C. Protect from moisture.

Keep in a safe place out of the reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very common	Allergic skin reaction (including rashes, hives and itching)		√	
Common	Hypotension (low blood pressure)		√	
Uncommon	Chest pain		√	
	Eosinophilia (abnormal white blood cell count)		√	
	Hyperparathyroidism (enlarged parathyroid glands)		√	
	Hypocalcemia (low blood calcium levels)		√	
	Osteoporosis (Bone Disease)		√	
	Peripheral edema (swelling of limbs)		√	

This is not a complete list of side effects. For any unexpected effects while taking FOSRENOL, contact your doctor or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be provided by contacting the sponsor, Shire Canada Inc. at: 1-800-268-2772.

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