

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-468

Approved Labeling

FOSRENOL® (foss-wren-all)

(Lanthanum Carbonate) 250 mg and 500 mg Chewable Tablets.

DESCRIPTION

FOSRENOL® contains lanthanum carbonate (2:3) hydrate 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 (La) is a naturally occurring rare earth element. Lanthanum carbonate is practically insoluble in water.

Each FOSRENOL®, white to off-white, chewable tablet contains lanthanum carbonate hydrate equivalent to 250 or 500 mg of elemental lanthanum and the following inactive ingredients: dextrans (hydrated) NF, colloidal silicon dioxide NF, magnesium stearate NF, and talc USP.

CLINICAL PHARMACOLOGY

Patients with end stage renal disease (ESRD) can develop hyperphosphatemia that may be associated with secondary hyperparathyroidism and elevated calcium phosphate product. Elevated calcium phosphate product increases the risk of ectopic calcification. 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. FOSRENOL® does not contain calcium or aluminum.

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:

Absorption/Distribution:

Following single or multiple dose oral administration of FOSRENOL® to healthy subjects, the concentration of lanthanum in plasma was very low (bioavailability <0.002%). Following oral administration in ESRD 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 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.

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

In 105 bone biopsies from patients treated with FOSRENOL® 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.

In studies in mice, rats and dogs, lanthanum concentrations in many tissues increased over time and were several orders of magnitude higher than plasma concentrations (particularly in the GI tract, bone and liver). 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.

Metabolism/Elimination:

Lanthanum is not metabolized and is not a substrate of CYP450. *In vitro* metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40 µg/ml does not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, and 3A4/5). 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 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 µg), renal clearance was less than 2% of total plasma clearance. Quantifiable amounts of lanthanum were not measured in the dialysate of treated ESRD patients.

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:

Lanthanum carbonate is neither a substrate nor an inhibitor of CYP450 enzymes.

The absorption of a single dose of 1000 mg of FOSRENOL® is unaffected by co-administration of citrate. No effects of lanthanum were found on the absorption of digoxin (0.5-mg), metoprolol (100-mg), or warfarin (10-mg) in healthy subjects co-administered lanthanum carbonate (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of coadministration). Potential pharmacodynamic interactions between lanthanum and these drugs (e.g., bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies was 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.

Clinical Trials:

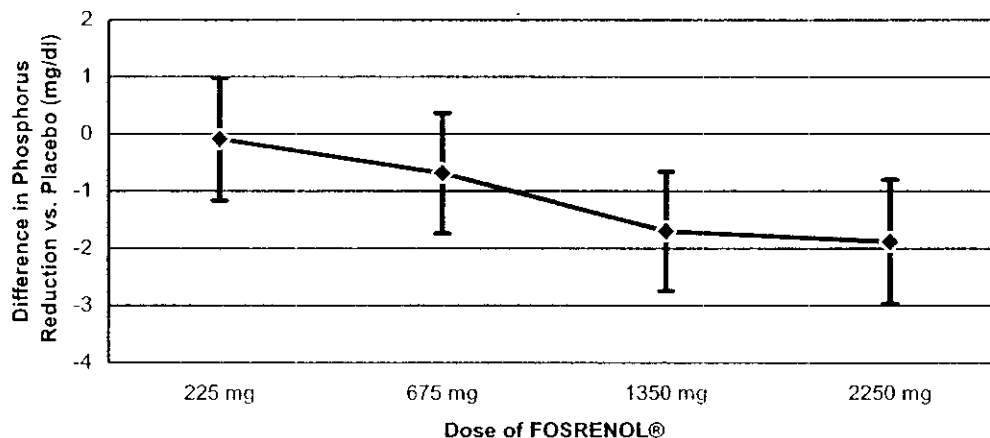
The effectiveness of FOSRENOL® in reducing serum phosphorus in ESRD patients was demonstrated in one short-term, placebo-controlled, double-blind dose-ranging study, two placebo-controlled randomized withdrawal studies and two long-term, active-controlled, open-label studies in both hemodialysis and 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 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 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 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 4.2 and 5.6 mg/dl in one study (doses up to 2250 mg/day) or ≤ 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 1.9 mg/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 2028 patients with ESRD undergoing hemodialysis. Patients were randomized to receive FOSRENOL® or alternative phosphate binders for up to six months in one study and two years in the other. The daily FOSRENOL® 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 FOSRENOL® in long-term, open label extensions.

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.

Paired bone biopsies (at baseline and at one or two years) in 69 patients randomized to either FOSRENOL® or calcium carbonate in one study and 71 patients randomized to either FOSRENOL® 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 FOSRENOL® or alternative therapy was 6.6%.

INDICATIONS AND USAGE

FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General:

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in FOSRENOL® clinical studies. Caution should be used in patients with these conditions.

Long-term Effects:

There were no differences in the rates of fracture or mortality in patients treated with FOSRENOL® compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that FOSRENOL® does not affect the risk of fracture or mortality beyond 3 years.

Information for the Patient:

FOSRENOL® tablets should be taken with or immediately after meals. Tablets should be chewed completely before swallowing. Intact tablets should not be swallowed.

Drug Interactions:

FOSRENOL® is not metabolized.

Studies in healthy subjects have shown that FOSRENOL® does not adversely affect the pharmacokinetics of warfarin, digoxin or metoprolol. The absorption and pharmacokinetics of FOSRENOL® are unaffected by co-administration with citrate-containing compounds (see **CLINICAL PHARMACOLOGY: In Vitro/In Vivo Drug Interactions**).

An *in vitro* study showed no evidence that FOSRENOL® forms insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril in simulated gastric fluid. However, it is recommended that compounds known to interact with antacids should not be taken within 2 hours of dosing with FOSRENOL®.

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 maximum recommended daily human dose (MRHD) of 5725 mg, on a mg/m² 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.

Pregnancy:

Pregnancy Category C. 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.

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.

Labor and Delivery

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

Nursing Mothers:

It is not known whether lanthanum carbonate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSRENOL® is administered to a nursing woman.

Geriatric Use:

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

Pediatric Use:

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 this population is not recommended.

ADVERSE REACTIONS

The most common adverse events for FOSRENOL® were gastrointestinal events, such as nausea and vomiting and they generally abated over time with continued dosing.

In double-blind, placebo-controlled studies where a total of 180 and 95 ESRD patients were randomized to FOSRENOL® and placebo, respectively, for 4-6 weeks of treatment, the most common events that were more frequent ($\geq 5\%$ difference) in the FOSRENOL® group were nausea, vomiting, dialysis graft occlusion, and abdominal pain (Table 1).

Table 1. Adverse Events That Were More Common on FOSRENOL® in Placebo-Controlled, Double-Blind Studies with Treatment Periods of 4-6 Weeks.

	FOSRENOL® % (N=180)	Placebo % (N=95)
Nausea	11	5
Vomiting	9	4
Dialysis graft occlusion	8	1
Abdominal pain	5	0

The safety of FOSRENOL® was studied in two long-term clinical trials that included 1215 patients treated with FOSRENOL® and 943 with alternative therapy. Fourteen percent (14%) 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 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. In Table 2, Study A events have been adjusted for mean exposure differences between treatment groups (with a mean exposure of 0.9 years on lanthanum and 1.3 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.71.

Table 2. 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=676)	FOSRENOL® (N=533)	Calcium Carbonate (N=267)
Nausea	36	28	16	13
Vomiting	26	21	18	11
Dialysis graft complication	26	25	3	5
Diarrhea	23	22	13	10
Headache	21	20	5	6
Dialysis graft occlusion	21	20	4	6
Abdominal pain	17	17	5	3
Hypotension	16	17	8	9
Constipation	14	13	6	7
Bronchitis	5	6	5	6
Rhinitis	5	7	7	6
Hypercalcemia	4	8	0	20

OVERDOSAGE

There is no experience with FOSRENOL® 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. In clinical trials, daily doses up to 4718 mg/day of lanthanum were well tolerated in healthy adults when administered with food, with the exception of GI symptoms. 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.

DOSAGE AND ADMINISTRATION

The total daily dose of FOSRENOL® should be divided and taken with meals. The recommended initial total daily dose of FOSRENOL® is 750-1500 mg. The dose should be titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Serum phosphate levels should be monitored as needed during dose titration and on a regular basis thereafter.

In clinical studies of ESRD patients, FOSRENOL® doses up to 3750 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.

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

HOW SUPPLIED

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